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VALUE OF BIOPSY OF THE LIVER IN NUTRITIONAL DYSTROPHY

Evaluation of Treatment with Choline and Dried Stomach

JULIO MENEGHELLO, M.D.

JULIO ESPINOZA, M.D.
AND
LILA CORONEL, M.D.
SANTIAGO, CHILE

THIS PAPER deals with the results of biopsies of the liver in infants with nutritional dystrophy. Gillman and Gillman,[1] in South Africa, published similar experiences in infantile pellagra. These authors checked the therapeutic efficiency of dried stomach, liver extract and vitamin B by biopsy of the liver. We used choline and dried stomach in treatment of the present series.

The clinical syndrome to be discussed is called "polycarencial dystrophy" in Chile, "specific dermatosis" in Uruguay and "beriberic pelagroid" in Cuba. In Mexico, the syndrome is called "culebrilla (snakeskin)." In the United States the terms "nutritional edema" and "hydropigenous multideficiency dystrophy" are used.

These "polycarencial (multiple deficiency)" dystrophies appear generally in infants over 1 year of age and occur frequently in countries with deficient hygienic conditions. The history of these patients reveals inadequate protein intake, excessive carbohydrate feeding and little or no consumption of fat. Vitamins are absolutely insufficient. As a rule, these children are brought to the clinics because of edema, which may be generalized, but more frequently appears in "shoelike" form on the lower and in "sleevelike" form on the upper extremities. The cheeks may also be edematous, and, at first glance, the children appear to be well nourished. The skin is usually dry and hyperkeratotic. Leukoderma and/or hyperpigmentation may be observed. Excessive perspiration, hypertrichosis and furunculosis are frequent observations

From the Manuel Arriaran Children's Hospital.

1. (*a*) Gillman, T., and Gillman, J.: Hepatic Damage in Infantile Pellagra and Its Response to Vitamin, Liver and Dried Stomach Therapy as Determined by Repeated Liver Biopsies, J. A. M. A. **129**:12 (Sept. 1) 1945. (*b*) Gillman, J., and Gillman, T.: Structure of Liver in Pellagra, Arch. Path. **40**:239 (Oct.) 1945. (*c*) Gillman, T., and Gillman, J.: Treatment of Infantile Pellagra, Lancet **2**:446 (Sept. 28) 1946.

in the patients. The tongue is red and the papillae are atrophic. The hair is pale and depigmented, especially in the temporal region and in the eyebrows. The liver is sometimes enlarged. The patients are apathetic; their faces are inexpressive, but, from time to time, they have irritable moments. Anorexia is common and the occurrence of vomiting and diarrhea is frequent during the first days in the hospital. The avitaminoses are subclinical. Scurvy may be detected with Kajdi's test and no roentgenologic examination, and vitamin A deficiency by demonstration of keratinization of the cornea. Hypoproteinemia and anemia are the rule. Osteoporosis is a constant observation on roentgenologic examination.

The "polycarencial" syndrome shows a clinical picture of varied symptoms, produced by insufficient intake of vitamins and nutritional elements indispensable for cellular metabolism (amino acids, fatty acids).

It has been suggested that the liver may be involved in the pathogenesis of the "polycarencial" syndrome. Only on serial biopsies of the liver could it be clearly established that the fatty degeneration constitutes a constant characteristic of the syndrome in children, with less frequent occurrence in adults, except in acute attacks. The fatty liver develops in the early stage of the disease, occasionally without complications.

From the results of biopsies in pellagrous children, the Gillmans [1a] classified the fatty changes of the liver into three grades according to the histologic picture:

Grade 1: Degeneration involves all hepatic cells, and they each contain a large drop of fat, the nucleus being displaced toward the periphery. In some specimens infiltration of round cells into the portal-biliary spaces is observed.

Grade 2: Nearly all cells contain various-sized droplets of fat, with some cells like those of grade 1. Other cells show large vacuoles in which only the cellular outline can be distinguished.

Grade 3: Most of the cells are free of fat. Where fat is present, it is in fine, powder-like particles. Sometimes, a few drops of fat the size of the nucleus, or larger, may be seen.

We have accepted this classification for our presentation.

TREATMENT

Treatment of the "polycarencial" syndrome was based on compensation for the nutritional deficiency by administration of proteins and vitamins. For this reason, several authors prescribed the most complete alimentation, rich in proteins, combined with blood and plasma transfusions, and vitamins, especially vitamin B.

In 1945, the Gillmans published a paper [1a] describing the treatment of pellagrous children with vitamins, liver extract and dried stomach.

This paper stated, that, while the disease is caused by nutritional deficiency, the secondary lesions, e. g., fatty liver, cannot be cured simply by additional supplementary alimentation. These authors demonstrated that vitamins of the B complex do not produce a favorable influence; on the contrary, these vitamins may intensify the hepatic lesions and cause the death of the patient. The authors considered that liver extract was indicated, but they observed that the reaction on treatment with it is slow and incomplete; biopsy specimens of the liver in "cured" patients still showed fatty degeneration, and clinical relapses were frequent.

The Gillmans were of the opinion that dried stomach is the treatment of choice in this picture and that its action, clinical as well as histologic, is fast and positive. In relation to such treatment, it should be recalled that gastrogenic pellagra was observed in gastrectomized men and swine. In addition, endogenous pellagra originating from a gastric lesion does not react to nicotinic acid but improves rapidly with administration of dried stomach.[1a]

The conclusion of the Gillmans that pellagra of dietetic origin is due to the alteration of a hepatogastric complex may be accepted. They also stated that the dried stomach acts through the presence of choline and that a complementary factor exists in the liver.

In a recent paper,[1c] the Gillmans again compared the curative effect of vitamins and dried stomach. They reemphasized the efficacy of the latter material. Hydrolyzed proteins were considered ineffective and dangerous, because in some patients they caused severe symptoms of intoxication, such as shock and hyperpyrexia.

MATERIAL

Our material consisted of 31 patients between 4 and 30.5 months of age, the average age being 14.6 months. These patients were distributed in three groups according to the treatment they received.

Group A was formed by 11 infants treated with complete alimentation and additional dried stomach U. S. P., prescribed in doses of 10 grains (0.65 Gm.) daily, diluted in 100 cc. of distilled water, plus 5 cc. of tenth-normal hydrochloric acid. This mixture has a disagreeable taste and many patients refused it. The dried stomach was administered for a minimum period of four days and maximum of ten days.

Group B comprised 14 patients to whom, besides complete alimentation, choline chloride in juice was given. The dosage was 5 grains (0.32 Gm.) daily for periods determined by the degree of control of the fatty degeneration of the liver seen on biopsies; administration was discontinued when the signs of grade 3 appeared. This drug has an agreeable taste and is easy to administer. The minimum period it was given was one to four days (because the patients died) and the maximum fifty-three days.

Group C consisted of 6 patients used as controls for the two preceding groups and treated exclusively with complete alimentation.

METHOD

Patients were examined carefully after their admission to the hospital and checked clinically every two days. The examination of every patient was completed by the following laboratory tests: complete blood count, blood sugar and cholesterol determination and hepatic function tests (the Takata-Ara, Hanger and prothrombin tests).

As a general rule, these tests were repeated after two weeks, together with the biopsy. In every patient roentgenograms were made, and in patients in whom rickets or scurvy was detected, adequate treatment was started. Urine and stool analyses were made routinely.

In taking the specimen for biopsy, we used the Silverman needle exclusively by the abdominal approach. In order to prevent hemorrhagic accidents in the removal of tissue for biopsy, it was necessary to control the values of coagulation, bleeding and prothrombin times. Tissue was not removed without previous trans-

TABLE 1.—*Frequency of Hepatic Lesions*

Fatty Degeneration	No. of Patients	Amount of Fat				Size of Fat Droplets			
		+++	++	+	±	Large	Medium	Small	Mixed
Grade 1	26	25	1	..	..	18	..	..	8
Grade 2	26	6	18	2	..	2	..	2	23
Grade 3	30	..	3	25	2	3	..	10	17

TABLE 2.—*Clinical Symptoms and Fatty Degeneration in the Liver*

Fatty Degeneration	Clinical Impression of Illness			
	Severe		Moderate	
	Number	Percentage	Number	Percentage
Grade 1	10	83	8	72
Grade 2	1	8	3	28
Grade 3	1	8	..	..

fusions in patients in whom intense anemia existed. The specimen was taken as soon as possible after admission. In some patients the poor general condition first required emergency treatment.

The first biopsy was made, on an average, the seventh day after admission, with a minimum period of two and a maximum of thirty days, in which time conditions shown on previous tests were normalized. Biopsy was generally repeated after twelve days and sometimes at less regular intervals because of intercurrent diseases. The shortest time interval between two biopsies was six days.

With reference to alimentation, we followed a general schedule, beginning with acidified milk and continuing with cow's milk. Little by little, the diet was given according to the child's reactions. Vitamins C and D were administered when symptoms of scurvy or rickets were suspected. Vitamin B was not prescribed because of the experience of the Gillmans.

Administration of dried stomach and choline was instituted after the first biopsy, so that the results of biopsy served as a control of the treatment.

Eighty-nine specimens for biopsy were taken from 29 patients in one year. Only in 3 cases did we fail to obtain tissue. There was no accident of importance.

In some infants, severe meteorism formed after the removal of tissue; in 4 patients this was accompanied with moderate fever. These symptoms disappeared within forty-eight to seventy-two hours without special treatment. It was proved on necropsy that the 4 deaths were not caused by the taking of the biopsy specimen a few days before. The point where the needle had penetrated the liver presented a small, pointed depression, apparently only of Glisson's capsule.

We used hematoxylin and sudan III to stain the fat. With the exception of 1 infant, we observed in all patients a fatty degeneration of the liver. In this 1 patient in whom no fatty degeneration existed, we observed a hydropic degeneration. We followed, along general lines, the Gillman classification as described previously. The characteristic histopathologic lesions in each grade were as follows:

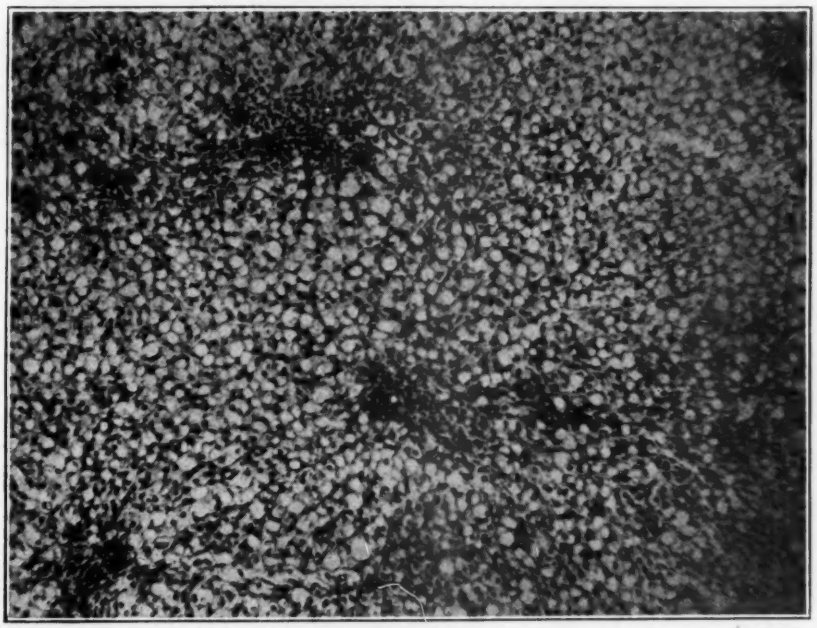

Fig. 1.—Photomicrograph showing characteristics of grade 1 fatty degeneration of the liver; intense degeneration; large droplets of fat; loss of structure; portal-biliary infiltration; proliferation of Kupffer cells; × 90.

Grade 1: Diffuse fatty degeneration in the form of large, profusely distributed drops, in some specimens combined with medium-sized and small droplets; closed sinuses or infiltrations of the portal-biliary spaces.

Grade 2: Fat in regular quantity distributed in droplets of all sizes; closed sinuses; infiltration of the portal-biliary spaces, and regular proliferation of the Kupffer cells.

Grade 3. Small quantities of fat in the form of small drops, sometimes combined with large and medium-sized drops; vacuolized cells which indicated reabsorption of the fat; inflammatory infiltration of the portal-biliary spaces, and proliferation of the Kupffer cells, the last two conditions being more frequent in this than in the other categories.

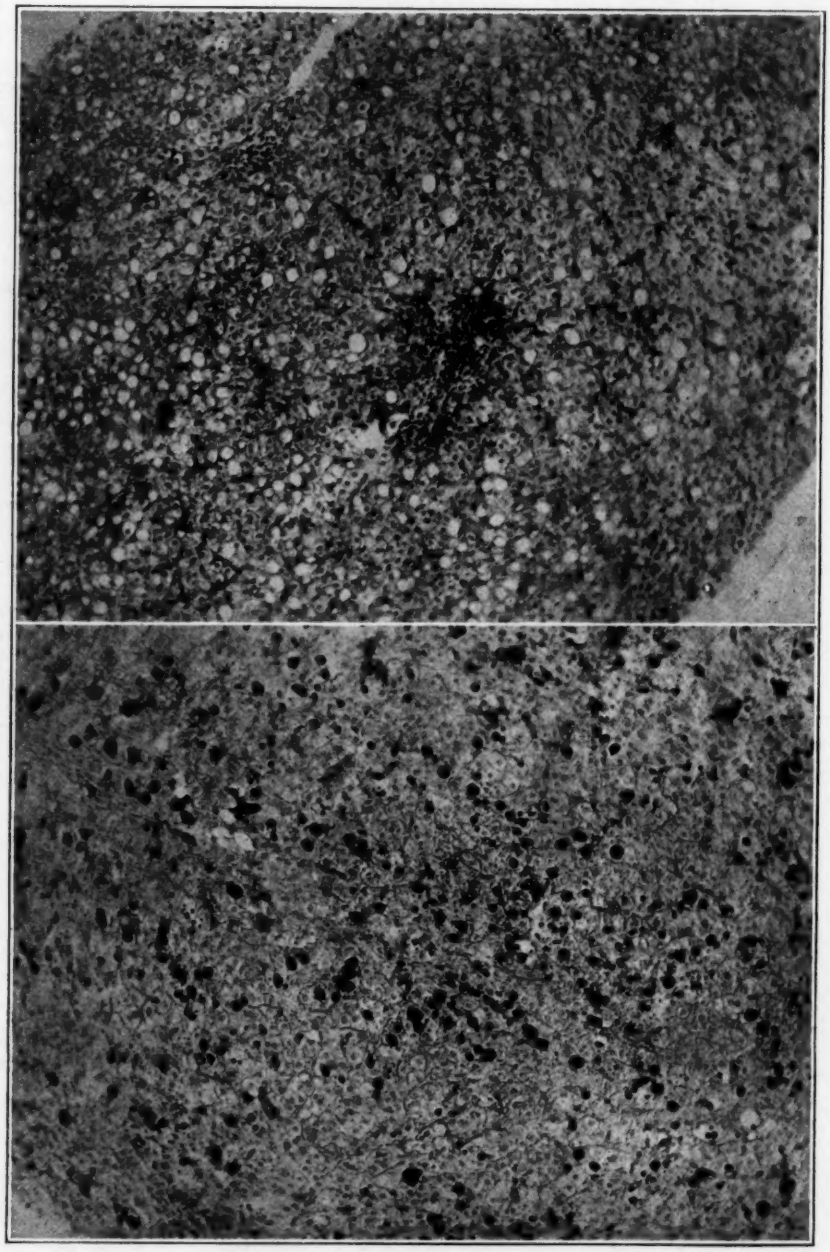

Fig. 2.—Photomicrographs showing characteristics of grade 2 fatty degeneration of the liver: Upper, moderate intensity of degeneration; variable size of fat droplets; visible structure; low grade portal-biliary infiltration; × 90. Lower, variable size of fat droplets with larger ones predominating; stained with sudan III; × 90.

CLINICAL RESULTS

We considered in serious condition all patients whose history showed frank subnutrition, and who were in bad general condition with mental involvement, atrophy of subcutaneous fat tissue or serious loss of weight, edema, intense nutritional deficiency and neurocutaneous symptoms. Less severely affected patients gave a history of malnutrition. Physical examination revealed only slight deviation from normal, little change psychically, conservation of the panniculus or no pronounced loss of weight, edema and few or no symptoms of nutritional deficiency.

Fig. 3.—Photomicrograph showing characteristics of grade 3 fatty degeneration of the liver; cytoplasm is clear; vacuoles of fat are few and small; × 90.

Of 29 such patients, fatty liver was observed in 28. Eighteen (78.2 per cent) had fatty changes of grade 1, 4 of grade 2 and only 1 of grade 3.

We observed, both in the seriously and the less severely affected patients, a high percentage of grade 1 (83.3 and 72 per cent, respectively) changes. The grade 2 changes were more frequent in the less severely diseased patients than in the seriously affected ones. The only seriously affected patient with grade 3 lesions had obstructive jaundice, whooping cough and bronchopneumonia as complications. The serious condition of this patient could be attributed to these diseases rather than to the nutritional syndrome itself.

We accepted three grades of clinical improvement when discharging the patients from the hospital: (*a*) slight recovery with gradual disap-

pearance of the edema and slight general improvement; (*b*) pronounced improvement or nearly complete recovery, with the aforementioned conditions, plus good appetite, normal feces and increasing weight; this degree of improvement is the most important, since it is followed by complete recovery; (*c*) complete recovery, with, in addition to the signs of grades *a* and *b*, excellent general and psychic conditions.

Analyzing the data given in table 3, we see that of 23 patients admitted with fatty degeneration of the liver, 17 recovered completely, 3 died and 3 reached only pronounced improvement or nearly complete recovery during the period of observation, which fluctuated between seventy-two and one hundred and sixty-three days. In the patients in whom complete

TABLE 3.—*Hepatic Degeneration and Clinical Improvement*

			Fatty Degeneration		
			Grade		
Clinical Diagnosis	Improvement		1	2	3
Severe	+++	No. of patients	4	1	1
	++		3	..	..
	Death		3	..	..
Moderate	+++		8	3	..

TABLE 4.—*Improvement of Hepatic Degeneration and the Clinical Picture*

	Improvement of Fatty Degeneration			Clinical Improvement		
Number of Patients	Grade 1	2	3	++	+++	Death
4	4	..	..	1	..	3
2	..	2	..	..	2	..
22	..	..	22	2	20	..

recovery was reached, this period was no longer than fifty-two days. The 3 children who died and the 3 who did not recover completely had fatty changes of grade 1 when admitted. However, the intensity of the hepatic disease, *per se,* does not influence the clinical symptoms of the patients. We can see this from the fact that all the patients with grade 1 lesions and intermediate clinical gravity were restored completely. On the other hand, the clinical gravity, *per se,* does not indicate the prognosis for the patient, as the 2 seriously ill infants, in whom fatty changes of grades 1 and 2 existed, showed complete clinical improvement.

We were interested in the relationship between the intensity of the hepatic changes and their regression. We observed in the 23 patients with fatty liver that the regression of the hepatic lesion was complete in grade 2 and incomplete or slower when the hepatic damage was of maximal intensity. Though the histologic difference between grades 1

and 2 is not so remarkable as that between grades 1 and 3, we observed in our patients a notable difference in the regression of the fatty changes between the two first categories. Table 4 shows the parallelism between the regression of hepatic changes and the clinical improvement.

Of the 4 patients with grade 1 changes, 3 died and 1 showed only slight improvement. The other patients with lesions of grades 2 and 3 improved completely, except in 2 instances in which pulmonary tuberculosis was the cause of the failure.

TABLE 5.—*Clinical Improvement and Treatment*

Treatment	Number of Patients Treated	Improvement		Death
		++	+++	
Moderate				
Dried stomach	6	1	5	..
Choline chloride	6	..	6	..
Control	3	..	3	..
Severe				
Dried stomach	5	1	4	..
Choline chloride	6	2	3	1
Control	3	1	2	..

TABLE 6.—*Treatment and Time Required for Change to Grade 3 of Classification*

	Number of Patients	Days Required	
Dried stomach	5	15	Average 33.8 days
	6	37	
	7	35	
	8	18	
	10	46	
	11	52	
Choline	1	41	Average 26.5 days
	3	20	
	6	21	
	9	24	

Among the complete series in group A, the condition of 1 patient remained stationary, in group B that of 2 patients showed no change and 1 other patient died, while in group C, 1 patient died.

Clinical Improvement.—We may say that all the seriously ill patients (except 1, to whom small doses of choline were given) showed recovery from the picture of nutritional deficiency. This is evident when it is remembered that we designated improvement as complete when the general condition was satisfactory.

Considering that the small number of cases at our disposal did not permit us to differentiate as to degree of improvement brought about by each of the three types of treatment, we tried to determine whether

there was a difference in the rapidity of recovery. Table 6 shows the average time required for clinical improvement according to the various kinds of treatment.

This table shows that the patients treated with choline had a slower average for regression of hepatic damage than patients treated with dried stomach. This confirms the impression that clinical improvement in the syndrome is somewhat faster in patients who receive larger doses of choline.

We classified the involvement of hepatic function into three degrees: serious, average and light. We considered that no involvement existed in patients with prothrombin levels above 80 per cent of normal. We compared the results of hepatic function tests with the results of biopsies made on the same day or less than five days afterward.

TABLE 7.—*Relation Between Hepatic Lesion (Histologic) and Results of Tests of Hepatic Function*

Fatty Degeneration	Number of Patients	Damage to Hepatic Function			
		Slight	Regular	Severe	Normal
Grade 1	15	8	2	1	4
Grade 2	12	9	2	0	1
Grade 3	9	7	0	0	2

RELATIONSHIP BETWEEN HEPATIC DEGENERATION AND HEPATIC FUNCTION TESTS

The biopsies of the liver, in our experience, constituted a simple procedure of extraordinary value for the study of the nutritional dystrophy. The absence of accidents in the taking of 89 biopsy specimens permits us this affirmation.

Sydenstriker [2] suggested that fatty liver is an early phenomenon in pellagra and that fatty liver is related to the pathogenesis of the disease.

In the majority of the infants, the fatty degeneration of the liver was so extensive that only with difficulty could the structure of the organ be recognized. In 78 per cent, the quantity of degeneration was such that the histologic appearance resembled that of fat tissue. We must agree with the Gillmans that this lesion has an important place in the pathogenesis of the picture. This could explain a large portion of the manifestations of the syndrome, e. g., the hypoproteinemia and the alteration in hemopoiesis and in the metabolism of carbohydrates. The alteration in the metabolism of sugars produces an excessive transformation into lipids which the organism is unable to absorb and which are deposited in the liver.

We came to the conclusion that the prognosis must be based on the results of biopsy and the clinical observations. Only this combination gives the physician a true idea of the evolution of the disease.

2. Cited by Gillman and Gillman.[1a]

We observed frequently that clinical improvement preceded the regression of the hepatic damage, which remained in grade 1 some days after the general condition had notably improved (the edema disappeared; the child began to accept food; the feces became normal). On the other hand, when the clinical condition remained serious or became worse, the intense degree of damage to the liver persisted. Nevertheless, nearly half the patients had conditions of average clinical gravity and almost all improved (2 died).

This shows that the hepatic damage was an important lesion, but that it was so only in the few patients who died and those had precisely the livers showing the most serious changes. This means that, in patients in whom through greater resistance of the organism a condition of average severity existed, a favorable evolution may be expected in spite of an intense hepatic lesion.

RESULTS OF TREATMENT WITH DRIED STOMACH

Our results obtained with dried stomach differed greatly from those of the Gillmans. We do not know exactly whether this difference is due to the product we employed or to the fact that the clinical condition of the Gillmans' patients was not quite the same as the clinical condition of ours. The Gillmans presented a small series of 20 patients, among whom, in spite of the division into three small groups, an obvious variation in results from the different treatments can be seen.

The Gillmans stated in all their papers not only that dried stomach acts quickly and produces complete regression of the hepatic lesion, but that its clinical effect is really extraordinary, showing an increase of diuresis within four to forty-eight hours and reabsorption of edema fluid within four to five days. In our patients, we did not observe any of these notable effects with this material.

The therapeutic results in our 29 patients gave the impression that in several of those serious ill the choline produced a faster improvement than by the dried stomach and the all-inclusive alimentation. In those patients the effect of the drug did not differ greatly from that of the alimentation. In patients with illness of medium gravity no difference in results from these three kinds of treatment existed. We agree with the Gillmans that these patients were cured with whatever treatment was given.

CONCLUSIONS

The taking of 89 specimens of liver for biopsy without any accident from 29 patients with nutritional dystrophy is reported. Intense hepatic fatty degeneration was proved consistently.

The clinical evolution depends in great part on the relation between the condition of the patient and the degree of hepatic damage. Neither of these elements alone permits a safe prognosis.

The fatty degeneration of grade 1 has a slower and less complete regression than that of the grade 2. The changes of grade 3 represent a residual lesion.

Clinical improvement generally precedes the regression of the hepatic lesions. No difference in the clinical course of hepatic improvement existed among patients treated with dried stomach, choline and all-inclusive alimentation.

It is proved that no parallelism exists between the functional involvement and the intensity of the hepatic damage.

Manuel Arriaran Children's Hospital, Santiago, Chile.

DISSEMINATED VISCERAL LESIONS ASSOCIATED WITH EXTREME EOSINOPHILIA

Pathologic and Clinical Observations on a Syndrome of Young Children

WOLF W. ZUELZER, M.D.
AND
LEONARD APT, M.D.
DETROIT

AMONG the conditions associated with pronounced and persistent eosinophilia of the blood there is an obscure group of disorders reported under various names, such as chronic eosinophilia,[1] eosinophilia leukemoides,[2] extreme eosinophilia and leukocytosis,[3] eosinophilia and splenomegaly,[4] Loeffler's syndrome [5] and others. Many cases of so-called eosinophilic leukemia and some instances of familial eosinophilia [6] evidently belong in the same ill defined category. Clearcut criteria for a clinical syndrome embracing the entire group have not been established, and few pathologic studies of pertinent cases are available. The diagnosis is, therefore, often difficult.

Prompted by a chance observation made in the course of an autopsy, we studied biopsy specimens of liver obtained from 3 patients with excessive eosinophilia and observed a characteristic widespread lesion which seems to us to represent the anatomic substrate of a clinical

From the Department of Pathology and the Anemia Clinic, Children's Hospital of Michigan, and the Department of Pathology, Wayne University College of Medicine.

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entity. We present the pathologic findings, together with clinical observations and with the results of certain laboratory tests, in the hope of contributing to the definition and diagnosis of this entity.

REPORT OF CASES

In 1942, in the course of a postmortem examination on the body of a 3 year old girl, one of us (W. W. Z.) encountered peculiar hepatic

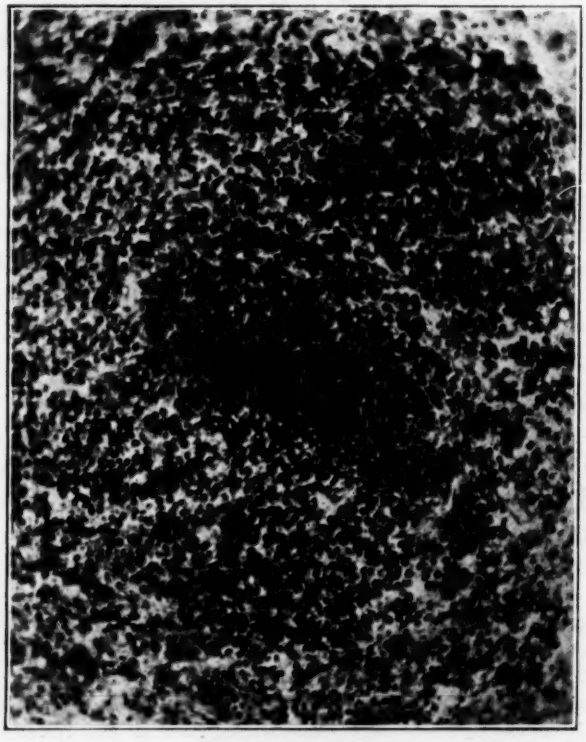

Fig. 1 (case 1).—Area of focal necrosis surrounded by diffuse infiltrations with eosinophilic leukocytes in liver. Hematoxylin and eosin stain.

granulomatous lesions which, up to that time, had not been reported in the literature.

CASE 1.—The patient, a white child who had previously been in excellent health and who had received no drugs or injections at any time, contracted a cold three weeks prior to her admission to the hospital. The symptoms consisted of coryza and wheezing respirations. The child seemed otherwise well until a few hours before her admission when, shortly after a meal, she began to vomit, quickly lost consciousness and had frequent generalized convulsions of clonic type. She was admitted in coma and was feverish and cyanotic, but the results of physical examination were otherwise normal. Urinalysis revealed no abnormalities, and the spinal fluid was normal as regards pressure, cell count and sugar

Fig. 2 (case 1).—Somewhat older lesion showing peripheral fibrosis and giant cell formation. Hematoxylin and eosin stain.

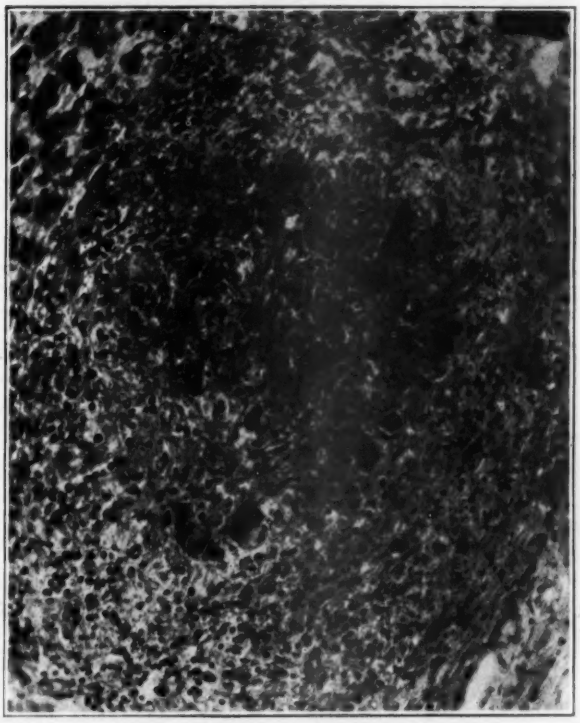

Fig. 3 (case 1).—Still more advanced lesion with small area of central necrosis surrounded by giant cells, histiocytes and fibrosis. Note diffuse infiltration with eosinophils in the stroma of the portal tracts. Hematoxylin and eosin stain.

and protein content. Within a few hours, the temperature had risen to 107.4 F., and the child died before any further procedures could be carried out.

A complete autopsy was performed, but an anatomic cause of death could not be shown. There were prominent swelling of the brain, pulmonary congestion and minimal, evidently terminal, bronchopneumonia present. Multiple nodular, flat or slightly raised gray areas were noted in the liver. These lesions were firm, sometimes gritty and usually, though not always, sharply circumscribed and ranged from 1 or 2 mm. to 1.5 cm. in size. The parenchyma between the lesions did not seem altered and size and weight of the organ were within normal limits. Cultures of the lesions yielded only Escherichia coli, evidently a contaminant. Cultures of heart's blood remained sterile.

Microscopic examination disclosed striking changes in the liver. The portal tracts in many areas were infiltrated with enormous numbers of eosinophil

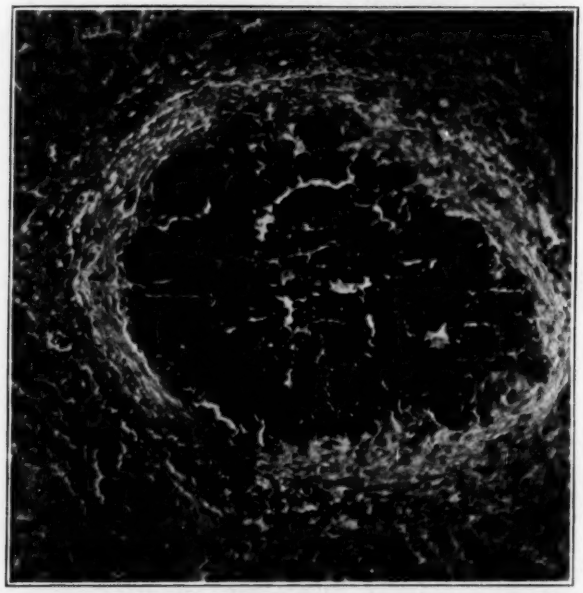

Fig. 4 (case 1).—Healed lesion showing central calcification and peripheral encapsulation. Von Kossa stain.

leukocytes. No other types of inflammatory cells participated in these infiltrations, which often seemed to spread widely into the adjacent parenchyma. Within the diffuse infiltrations there were areas of more or less sharply circumscribed necrosis. Other, obviously older, lesions consisted of necrotic centers surrounded by poorly formed palisades of histiocytes and by giant cells and fibroblasts. Still older lesions showed central fibrosis or calcification and were surrounded by well formed capsules of concentrically arranged collagen fibers. Nearly all these focal lesions could be shown to be within the connective tissue of Glisson's capsule, but no special relationship to arteries, veins or bile ducts was demonstrated. Rarely, the central or sublobular hepatic veins showed infiltrations of intima and adventitia with eosinophils and partial obstruction of the lumen by proliferating fibroblasts.

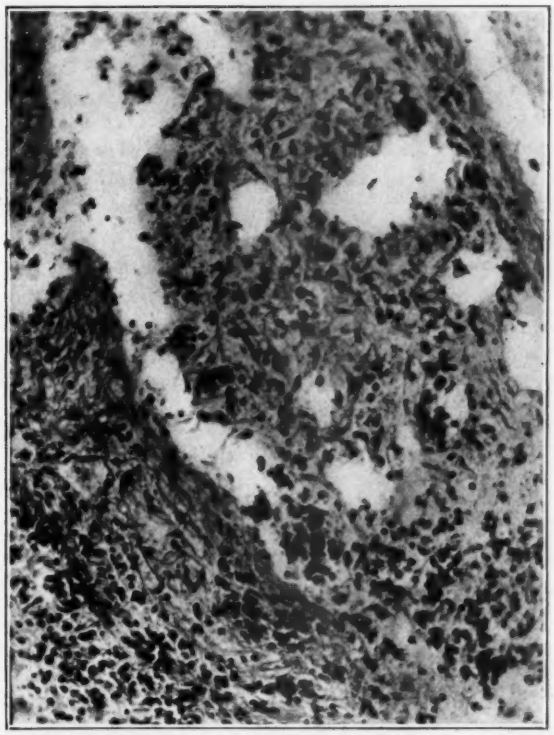

Fig. 5 (case 1).—Branch of hepatic vein showing endophlebitis and periphlebitis, with extensive eosinophilic infiltrations of both intima and adventitia and fibroblastic proliferation with partial obliteration of lumen. Hematoxylin and eosin stain.

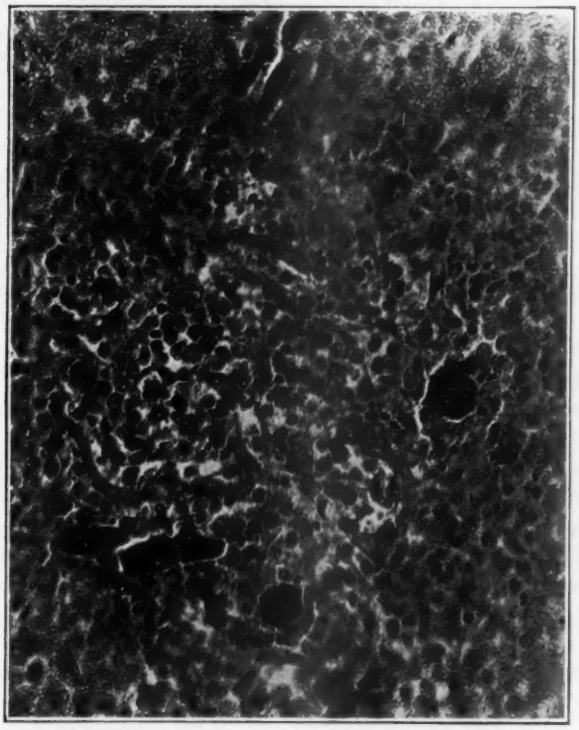

Fig. 6 (case 1).—Charcot-Leyden crystals among degenerating inflammatory cells. Safranine stain.

In both recent and old lesions peculiar refractile needle-shaped or hexagonal structures were seen in abundance. These needles were often surrounded by degenerating eosinophils or by giant cells and were identified as Charcot-Leyden crystals. Every effort to demonstrate bacteria, acid-fast bacilli, fungi, protozoa or other parasites or ova proved fruitless.

Mild infiltrations with eosinophils were noted in the mediastinal and mesenteric lymph nodes and in the spleen. The number of eosinophil granulocytes in the bone marrow appeared greatly increased. In the lung occasional eosinophils were seen to infiltrate the walls of the small branches of the pulmonary arteries, but no destructive lesions were observed. Nothing unusual was seen in sections taken from various areas of the brain.

Summary.—Fresh and old granulomatous lesions with eosinophilic infiltrations were observed in the liver of a 3 year old girl who died with symptoms of an encephalopathy after three weeks of rhinitis and asthmatic breathing. Although results of blood studies were not available, the presence of eosinophilia was strongly suggested by the character of the lesions and by the eosinophilia of the bone marrow.

A few years later the opportunity for further investigation of the problems posed by this case presented itself.

CASE 2.—James G., a Negro boy, was first admitted to the hospital at the age of 3 months in November 1944, because of cough, coryza, labored breathing and fever. Roentgenograms of the chest showed minimal infiltration in the left pulmonary field. Sulfadiazine was prescribed and prompt recovery ensued. At 5 months of age the child was readmitted because of suppurative cervical adenitis which was treated by incision and drainage. Again sulfadiazine was administered, and again the child made a good recovery. Thereafter, he returned frequently to the clinic and several times was readmitted to the hospital because of severe infections of the upper respiratory tract accompanied with fever and often with convulsions. Each time he received sulfadiazine with apparent benefit. Roentgenograms failed to show pulmonary infiltrations. Blood counts were done on numerous occasions, and the number of eosinophils was always within the normal range. A moderate hypochromic-microcytic anemia developed.

In September 1946, enlargement of the liver was noted for the first time. By now a soft systolic murmur had also been noted over the apex of the heart. The white blood cell count was 24,800 per cubic millimeter, with 40 per cent of the cells eosinophils. No ova or parasites could be discovered in the stools. Because of the unexplained hepatomegaly and eosinophilia and a persistent cough and intermittent fever the child was readmitted for further study on October 10.

Physical examination revealed a moderately ill 2 year old boy. The nostrils contained small amounts of mucopurulent exudate. The tonsils were large and cryptic. The left tympanic membrane was reddened. Small, shotty lymph nodes were palpable on both sides of the neck. The lungs appeared normal. A harsh apical systolic murmur over the precordium was described. The abdomen was protuberant, and the liver was palpable 2 fingerbreadths below the costal margin. The spleen was also stated to be enlarged. The skin was free of eruptions.

Roentgenograms showed slight enlargement of the cardiac silhouette but no changes in the pulmonary fields and no significant abnormalities in the skeleton.

TABLE 1.—*Data on Peripheral Blood and Bone Marrow Studies*

	Peripheral Blood												Bone Marrow																Family		
				Differential Count																											
Case No.	Hemoglobin Concentration, Gm.	Red Blood Cells, Millions	White Blood Cells, Thousands	Neutrophils, %	Lymphocytes, %	Myelocytes, %	Basophils, %	Eosinophils, %	Absolute Eosinophil Count, on Admission	Absolute Eosinophil Count, Highest Level	Absolute Eosinophil Count, Latest Level	Reticulocytes, %	Stem Cells	Pronormoblasts	Basophilic Normoblasts	Polychromatic Normoblasts	Orthochromatic Normoblasts	Lymphocytes	Monocytes	Promyelocytes	Myelocytes	Metamyelocytes	Band Forms	Neutrophils	Eosinophilic Myelocytes	Eosinophilic Band Forms	Eosinophils	Eosinophils, Total, %	Sed. Rates		No. of White	Blood Cells Eosinophils, %
2	10.1	3.8	24.8	16	43	1	0	40	9,800	15,400	90,500	...	....	0.5	1.0	13.5	2.0	20.5	...	1.0	1.5	3.5	6.5	13.0	8.0	6.5	22.5	37.0	3			
3	9.1	3.68	13.8	22	40	1	1	36	15,700	70,500	44,800	3.0	....	0.2	0.8	10.2	0.2	11.8	...	0.6	4.0	2.6	13.4	9.8	11.4	88	20.2	46.4	....	Mother	12,300	1
																														Father	19,800	2
																														Sister, see case 4		
4	13.2	4.94	11.9	35	43	2	0	20	2,300	2,500	1,300	...	....	....	....	....	....	....	...	...	...	...	....	....	....	....	....	....	....	See case 3		
5	9.6	4.15	98.4	1	11	1	0	87	85,600	92,700	75,500	2.5	....	0.4	1.6	6.6	....	7.8	...	2.0	1.2	1.4	13.2	17.4	11.8	13.6	24.8	54.2	51	Mother	7,800	3
																														Father	7,900	1
																														Sister	13,000	4
6	9.0	4.3	50.1	10	39	0	0	51	25,500	25,500	16,300	...	0.15	....	2.5	9.0	0.5	54	0.5	4.0	6.5	4.0	2.0	5.5	1.5	0	13	19.5	11.5			
7	9.2	3.25	72.0	44	25	4	0	27	19,400	40,300	104	0.7	1.6	0.6	0.8	9.8	....	20.8	1.2	0.4	1.2	4.2	6.4	16.6	3.0	....	18.2	21.2	....			
8	7.0	4.46	11.4	20	24	2	0	4	1,634	2,261	1,016	...	....	....	....	....	....	....	...	...	...	...	....	....	....	....	....	....	....	Mother	10,500	4

Urinalysis showed no abnormalities. The hemoglobin concentration of the blood was 10.0 Gm. and the red blood cell count 4,020,000. The white blood cell count was 27,500, and the differential count showed 56 per cent eosinophils, 16 per cent neutrophils, 26 per cent lymphocytes and 1 per cent monocytes. There was no sickling of the erythrocytes on wet preparations. The Mazzini test for syphilis gave a negative reaction. The intradermal tuberculin test and cutaneous tests with Trichincella, Ascaris and Histoplasma antigens elicited negative reactions. Repeated stool examinations showed mucus but no blood and no ova or parasites. A number of other laboratory tests are summarized in tables 1 and 2. A biopsy specimen of a cervical lymph node showed mild diffuse infiltration of the reticulum with mature eosinophils. A biopsy specimen of the gastrocnemius muscle revealed no abnormality.

TABLE 2.—*Chemic*

	Total Protein, Gm./100 Cc.	Albumin, Gm./100 Cc.	Globulin, Gm./100 Cc.	Albumin to Globulin Ratio	Serum Bilirubin, Mg./100 Cc.	Prothrombin, % of Normal	Alkaline Phosphatase, Bodansky Units	Serum Cholesterol, Mg./100 Cc.	Cephalin Flocculation	Thymol Turbidity, Units	Urinary Urobilinogen	Blood Agglutination Titers	Ova
2	6.9	3.84	3.06	1.3:1	0.8	51	...	...	1+	....	.....	.....	.....
	7.18	2.96	3.22	0.7:1	0.8	...	...	...	3+	....			
	....	....	....	.....	....	...	...	...	1+	....			
3	9.71	4.23	5.48	0.8:1	0.35	...	...	132	1+	....	Negative (1:10)	Heterophil: Positive (1:112)	
	10.13	3.72	6.41	0.5:1	....	...	...	...	...	....			
	10.35	3.42	6.93	0.5:1	....	...	...	...	...	....			
4	....	....	....	.....	0.43	109	6.4	133	Negative	0.255	Negative (1:10)	Heterophil, Brucella: Negative	
5	10.43	3.63	6.80	0.5:1	0.2	100	5.4	90	1+	....	Negative (1:40) Negative (1:20)	1 Typhoid O and H 2 Salmonella 3 Brucella: Negative	
6	8.46	....	....	.....	0.11	100	8.5	98	±	0.3	Positive (1:50)	Heterophil: Positive (1:56)	
	7.86	3.59	4.27	0.8:1	....	...	...	...	...	....	Negative (1:100)		
7	7.87	2.96	4.91	0.6:1	0.8	...	...	...	...	....	.....	.....	
8	9.49	3.64	5.85	0.6:1	0.16	100	4.6	105	±	0.74	Negative (1:10)	.....	

During the following year, hepatomegaly and cardiac murmur and enlargement persisted and the percentage of eosinophils in the white blood cell count remained between 30 and 60. The total white cell count fell however. The values for the absolute eosinophil counts are shown in figure 7. The child continued to have frequent attacks of coryza, cough and fever and occasional convulsions. He was again admitted in August 1947, now 3 years old. The physical and roentgenographic findings were unchanged. The white cell count was 10,000, with 30 per cent eosinophils. The reaction to the cephalin flocculation test was 1 plus. Again stools and this time also duodenal contents were examined for parasites or ova, with negative results.

In view of the findings in case 1 it was decided to perform a laparotomy for the purpose of visualizing the liver. At operation the liver was observed to be enlarged and studded with firm gray nodules, varying from 1 to 6 mm. in diameter. Microscopic study showed lesions similar to those encountered in case 1. The portal tracts were diffusely infiltrated with eosinophils and in places with lymphocytes which occasionally formed part of small lymphoid follicles. Within the eosinophilic infiltrations there were circumscribed areas of necrosis surrounded

by granulation tissue and giant cells. No parasites or micro-organisms could be seen.

Hexylresorcinol was given but no ascarides or ova were passed. The child was discharged and has remained under our observation until the present. Except for frequent episodes of cough and coryza he has remained well, although at the time of his last visit, in April 1949, hepatomegaly and cardiac findings persisted unchanged. The white blood cell count throughout this period remained within normal limits and the percentage of eosinophils slowly fell to 10.

Summary.—Eosinophilia, hepatomegaly and slight cardiac enlargement were present over a period of two and one-half years in a young Negro child who had innumerable attacks of coryza and bronchitis, fever

nd Immunologic Data

Ova and Parasites	Nasal Smear for Eosinophils	Cutaneous Reactions (Parasites)		Cutaneous Reactions (Common Allergens)	Antihelmintic Therapy	Nose and Throat Cultures
tools, negative uodenal contents, negative	.....	Trichinella Histoplasmin Ascaris	Negative	.....	Hexylresorcinol	.....
tools, negative uodenal contents, negative	Sputum with eosinophils	Trichinella Filaria Brucella Ascaris	Negative	No significant reactions	Hexylresorcinol Neoarsphenamine	Staph. albus Hemolytic strep. Nonhemolytic strep. Strep. viridans N. catarrhalis
tools, negative	Occasional eosinophils	Trichinella Ascaris	Negative	No significant reactions	.....	Staph. albus Hemolytic staph. albus Strep. viridans N. catarrhalis
tools, negative	Occasional eosinophils	Trichinella Ascaris Filaria Brucella	Negative	No significant reactions	.....	Staph. aureus Staph. albus Strep. viridans N. catarrhalis
tools, negative	Many eosinophils	Trichinella Ascaris Filaria	Negative	.....	.....	Staph. albus Strep. viridans N. catarrhalis D. pneumoniae
tools, negative	.....	.....	.....	.....	.....	.....
tools, negative	Negative	Trichinella	Negative	.....	.....	.....

and recurrent convulsions but was free of symptoms during the intervals. The child had been under observation during the first two years of life when neither eosinophilia nor hepatomegaly was present. At no time since the appearance of these findings were pulmonary infiltrations seen in roentgenograms, and there were no complaints suggestive of asthma or other allergic conditions. Hepatic function was not demonstrably impaired except for a transient lowering of the prothrombin concentration in the plasma and a positive reaction to the cephalin flocculation test, but the sedimentation rate was high and the plasma globulins were increased. All tests for parasites and for sensitivity to parasitic antigens gave negative reactions. Widely disseminated lesions, consisting of granulomas with necrotic centers, giant cells and diffuse eosinophilic infiltrations, were observed in the liver.

In the study of the next case, the preceding observations could be extended. This patient is of particular interest because eosinophilia was observed in a sibling as well.

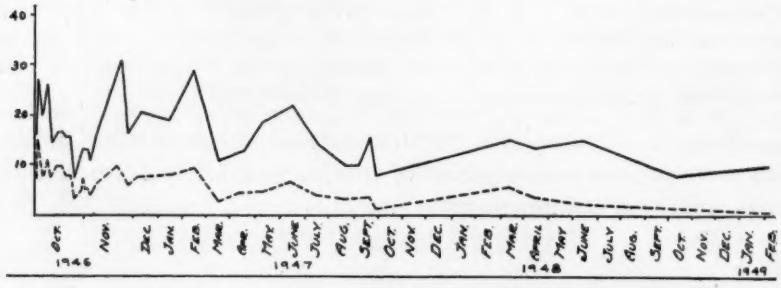

Fig. 7 (case 2).—Graph showing the total leukocyte count and the absolute number of eosinophils over two and one-half years in patient James G. The solid line represents the number of leukocytes (× 1,000) and the broken line, the number of eosinophils (× 1,000).

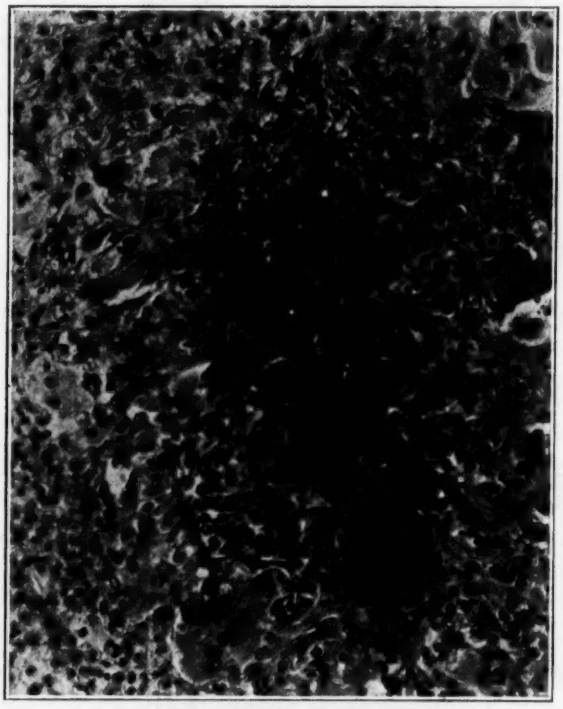

Fig. 8 (case 2).—Focal area of necrosis and granuloma formation with giant cells and histiocytes surrounded by diffuse eosinophilic infiltrations. Hematoxylin and eosin stain.

CASE 3.—Perilyn P. was an 18 month old white girl admitted to the hospital Oct. 7, 1948 because of a severe infection of the upper respiratory tract. The child had seemed well until three weeks earlier, when she began to cough and to

vomit frequently. During the last three days the cough had become worse and, for the first time, had been accompanied with wheezing. The stools had increased in number and were mucoid, thin and greenish. On the day of her admission the child seemed feverish and apathetic.

The patient was reared in metropolitan Detroit and had never left the city. Her diet had consisted of pasteurized milk, cereals, vegetables, meat, orange juice

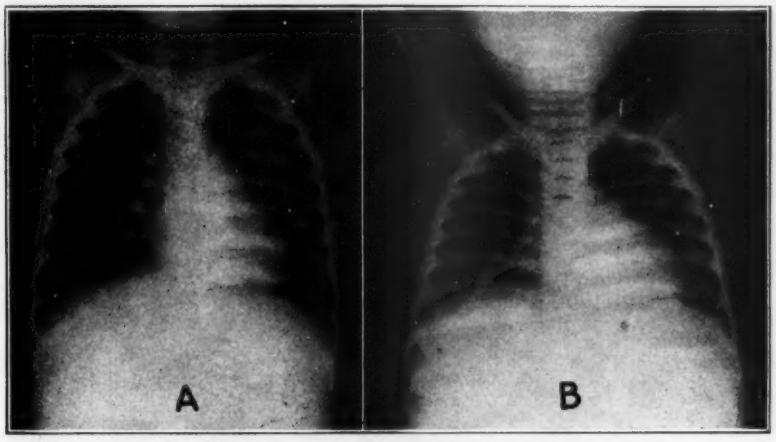

Fig. 9 (case 3).—Roentgenograms of thorax (*A*) taken on admission, showing infiltration in region of middle lobe of right lung and bilateral hilar infiltrations, and (*B*) taken ten days later, showing more extensive infiltrations.

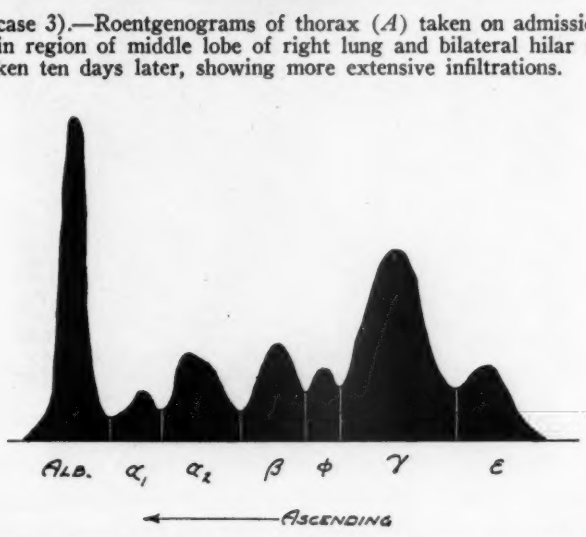

Fig. 10 (case 3).—Electrophoretic pattern of serum protein. Note the striking elevation of the gamma globulin. Total protein measured 10.35 Gm. per hundred cubic centimeters. Albumin was 26.8 per cent, α-globulin, 5.2 per cent, α_2-globulin, 12.6 per cent, β-globulin, 11.6 per cent, ϕ-globulin, 5.6 per cent, γ-globulin, 38.2 per cent, of total protein, and the albumin to globulin ratio 0.37.

and cod liver oil. No sensitivity to any of these foods had been noted. At the age of 11 days she had been admitted to this hospital because of loss of weight, anorexia and vomiting. At that time no abnormalities had been noted on physical examination and no eosinophilia had been present. The symptoms had subsided

immediately and thereafter the child had always eaten well and gained weight. At the age of 1 year she had measles without complications. She had never had symptoms referable to allergy in the usual sense. The family history was likewise negative for allergic manifestations.

The patient was acutely ill, lethargic and feverish. Her respirations were rapid and she coughed frequently. The nostrils were crusted with mucopurulent discharge. Rhonchi and musical rales were audible over the thorax. The heart appeared normal. The liver was decidedly enlarged to palpation, and it was thought that the spleen was likewise palpable.

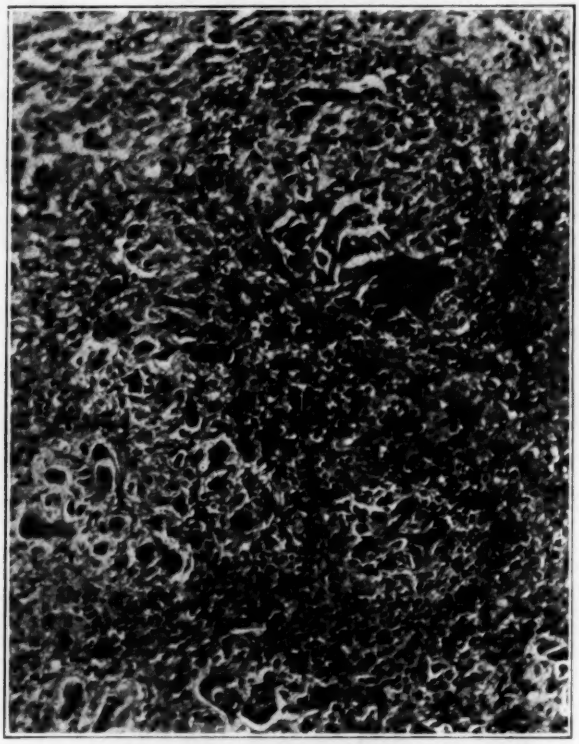

Fig. 11 (case 3).—Focal lesions showing granulomatous structures surrounded by eosinophilic infiltrations. Hematoxylin and eosin stains.

A roentgenogram (fig. 9 *A*) showed an area of consolidation in the region of the middle lobe of the right lung, bilateral hilar and peribronchial infiltration and generalized emphysema.

Urinalysis gave normal results. The hemoglobin concentration of the blood was 9.3 Gm., with 3,680,000 red blood cells and 43,000 white blood cells. Eosinophils constituted 36 per cent of the cells in differential counts. The reaction to the Mazzini test was negative. The reaction to an intradermal tuberculin test and the cutaneous reactions with Brucella, Trichinella and Ascaris antigens were likewise negative. Repeated examinations of stools, gastric juice and duodenal contents for parasites or ova gave negative results. The sputum contained many eosinophils.

The pertinent laboratory data are summarized in tables 1 and 2. The high levels of serum protein and the distortion of the electrophoretic pattern (fig. 10) are of particular interest.

After completion of the preliminary tests, a laparotomy was performed. The liver was studied with innumerable whitish lesions, a few millimeters in diameter, and decidedly enlarged. What had seemed to be an enlarged spleen was identified at operation as the left lobe of the liver.

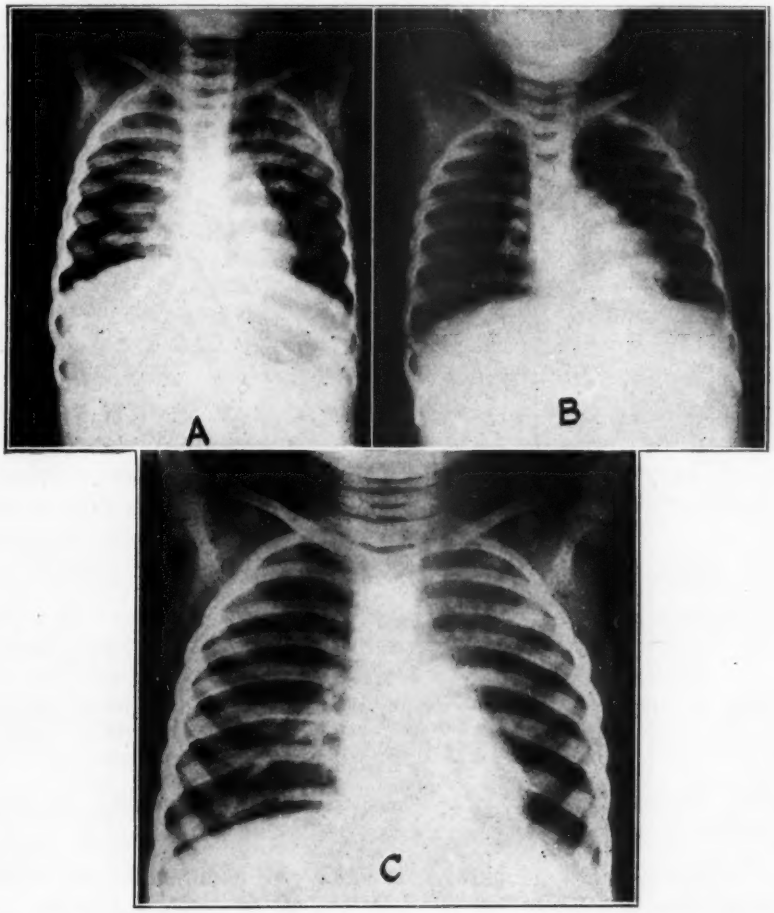

Fig. 12 (case 3).—Roentgenograms of thorax (*A*) showing further spread of pulmonary infiltrations taken three weeks after admission, (*B*) taken six weeks later showing clearing of pulmonary lesions, and (*C*) taken six months after onset. The patient was asymptomatic but eosinophilia and hepatomegaly persisted. Note recurrence of infiltrations involving upper lobe of left lung and lower lobe of right lung.

Microscopic examination showed diffuse infiltration of the portal triads with eosinophils and occasional lymphocytes. In addition, there were multiple focal tubercle-like granulomas originating in Glisson's capsule but spreading into adjacent parenchyma and consisting of eosinophils, plasma cells and giant cells grouped

around scanty fibrillar eosinophilic material. The lesions appeared to be of comparable age throughout. No crystals and no parasites or micro-organisms could be demonstrated with a variety of special stains. Fresh wet preparations of the crushed lesions failed to show larvae.

The subsequent clinical course was characterized by irregular fever of low grade, recurrence and spreading of pulmonary infiltrations, followed by resolution and appearance of new shadows in other parts of the lungs. The last of these recurrences was noted in March 1949, five months after the onset and while the patient was free of symptoms. She did, however, have frequent intermittent cough, coryza and wheezing respirations. Meanwhile, hepatomegaly and eosinophilia persisted unchanged.

Because of the favorable results reported in so-called tropical eosinophilia[7] with arsenotherapy the patient received three full courses of neoarsphenamine

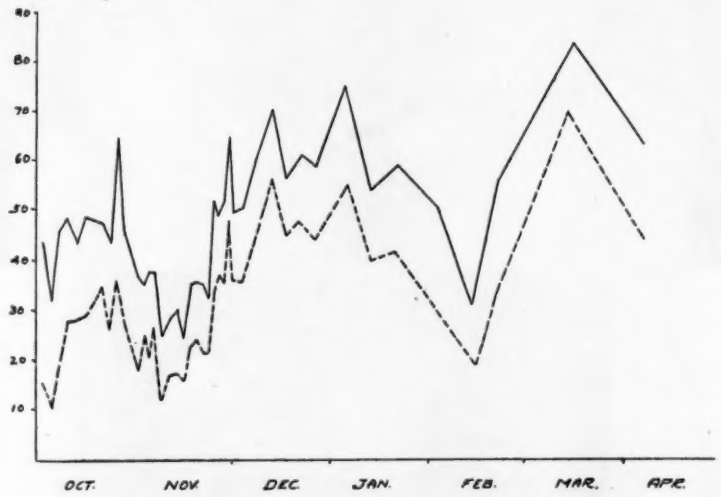

Fig. 13 (case 3).—Graph showing the total leukocyte count and the absolute number of eosinophils. The solid line represents the number of leukocytes (× 1,000) and the broken line the number of eosinophils (× 1,000).

without appreciable effect. Earlier administration of hexylresorcinol had failed to produce passage of any ova or parasites.

Summary.—An 18 month old white girl became ill with cough, coryza, asthmatic breathing and gastrointestinal symptoms. The outstanding findings consisted of rapidly changing recurrent pulmonary infiltrations, hepatomegaly, persistent eosinophilia, leukocytosis and hyperglobulinemia, all demonstrable over a period of six months' observation and not yielding to treatment with neoarsphenamine. A biopsy specimen of the liver revealed disseminated granulomatous lesions and eosinophilic infiltrations.

7. Hirst, W. R., and McCann, W. J.: Tropical Eosinophilia, U. S. Nav. M. Bull. **44**:1277, 1945.

Because of the observations on this patient, the blood of the parents and of the sister was examined. Nothing unusual was observed in the adults. The sister was demonstrated to have an eosinophilia and her case is, therefore, briefly reported.

CASE 4.—Penelope P., a 3½ year old girl, had never been ill and had not shown symptoms of asthma, hay fever, eczema, urticaria or other allergic manifestations. When seen on Oct. 23, 1948, she appeared slightly obese; the tonsils were hypertrophied, and the pharynx was slightly reddened. Roentgenograms of the chest showed only a slight increase in perihilar shadows but no infiltration. The white blood cell count was 11,900, and there were 20 per cent eosinophils. No parasites or ova were seen in several stool specimens. Cutaneous tests with Ascaris and other parasitic antigens likewise gave negative reactions. The pertinent tests are listed with their results in tables 1 and 2.

In the six months during which the patient has been under observation she has appeared entirely free of symptoms, yet the eosinophilia has remained stationary. At no time did the liver appear enlarged. Roentgenograms on several occasions have shown no significant changes in the lungs.

Summary.—Eosinophilia of fairly serious degree was demonstrated in the sister of a patient with eosinophilia and pulmonary infiltrations. This child had no symptoms, and no significant abnormalities could be shown in roentgenograms or on physical examination. No parasites or ova were found and no sensitivity to parasitic antigens could be demonstrated. Since earlier studies of the sister's blood and examination of the parent's blood had failed to show increased numbers of eosinophils, a familial hereditary eosinophilia was excluded.

The next case shows considerable similarity to cases 2 and 3.

CASE 5.—The patient, Alan C., was referred to the hospital in December 1948 because elsewhere a white blood cell count of 86,000 and eosinophilia of 80 per cent had been demonstrated. The child was a 2 year old white boy who had been ill with cough and wheezing for one month. The family physician had observed decided abdominal enlargement. After the onset of respiratory symptoms, transient urticarious swellings of the skin had been noted by the parents.

This child was brought up on a farm in Ontario, Canada, and had received an ample, varied diet, including raw milk which came from the father's own herd of cows. It was stated that there was brucellosis among the animals.

At the age of 4 months the child had had a mild attack of diarrhea. A month later he had a severe attack of "asthma" with wheezing respirations which lasted for several hours. Thereafter, he had wheezed with every infection of the respiratory passages. At 6 months of age he had a mild infection of the ear. Otherwise he had been in good health. He had never received sulfonamide drugs in any form.

The family history was noncontributory. Both parents and the 5 year old sister were in excellent health and had none of the usual allergic diseases. Blood studies in these 3 persons disclosed no eosinophilia.

The patient did not appear ill. Except for the presence of frothy mucus in the pharynx and pronounced enlargement of the liver with protuberance of the entire abdomen, the physical findings were not unusual. The temperature was

Fig. 14 (case 5).—Graph showing the total leukocyte count and the absolute number of eosinophils. The solid line represents the leukocytes (× 1,000) and the broken line, the eosinophils (× 1,000).

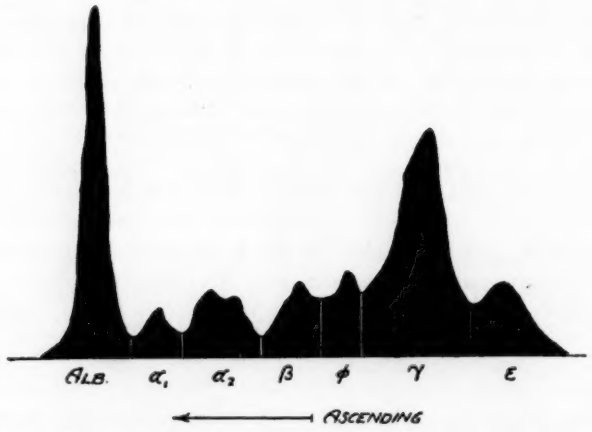

Fig. 15 (case 5).—Electrophoretic pattern of serum protein. Note the decided elevation of the gamma globulin. Total protein measured 10.6 Gm. per hundred cubic centimeters. Albumin was 28.4 per cent, α-globulin, 4.8 per cent, α_2-globulin, 10.3 per cent, β-globulin, 8.5 per cent, φ-globulin, 7.0 per cent, and γ-globulin, 41.0 per cent, of total protein, and the albumin to globulin ratio, 0.4.

normal. Roentgenograms of the chest revealed bilateral hilar and peribronchial infiltration, but no frank parenchymal shadows.

The white blood cell count on admission was 98,000, and on subsequent occasions it rose as high as 105,000. Eosinophils constituted 87 per cent of the total count, the remainder being lymphocytes, neutrophils and monocytes. The pertinent findings are shown in tables 1 and 2. Hyperglobulinemia was again a noteworthy feature. As before, every attempt to demonstrate an etiologic factor, including cutaneous tests and agglutination tests for brucellosis, was unsuccessful.

A laparotomy was performed, and the liver, as in cases 1, 2 and 3, was observed to be studded with grayish lesions. A piece containing a number of these lesions

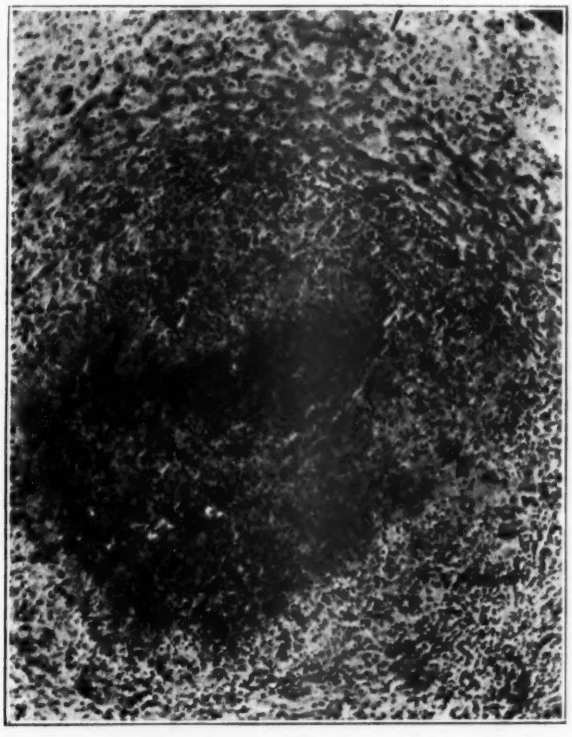

Fig. 16 (case 5).—Focal area of necrosis surrounded by a diffuse eosinophilic infiltration. Hematoxylin and eosin stain.

was removed and divided so that one part was used for cultures employing a variety of mediums. Another part was examined, after crushing in saline solution, for possible larvae, with negative results. A third portion was incubated for eight days and then examined with negative results. The remainder was used for histologic studies. The lesions were similar to those seen in the other cases but differed in that they appeared to represent an earlier phase of the pathologic process. The necrotic foci were not surrounded by giant cells or granulation tissue but only by a narrow rim of histiocytes followed by eosinophils. These changes resembled the fresh lesions observed in case 1. There were also numerous Charcot-Leyden crystals at the periphery of the necrotic foci. No ova, larvae, micro-organisms or fungi were found. Cultures taken from the original specimen,

including those grown on Sabouraud's medium and in anaerobic jars, remained sterile.

Mice inoculated intraperitoneally, subcutaneously and intrahepatically failed to die or show symptoms of any kind. The animals were killed at varying intervals up to one month. No lesions were observed in their tissues, and subinoculation of the tissues likewise failed to produce symptoms or lesions.

The patient has been followed for four months from the onset of symptoms. During this time he has had frequent colds accompanied with wheezing but has remained otherwise well. At no time were pulmonary shadows seen in roentgenograms of the chest. Eosinophilia, leukocytosis, hyperglobulinemia and hepatomegaly have persisted without change. No special therapy was employed. At the time of writing the child appears active and healthy.

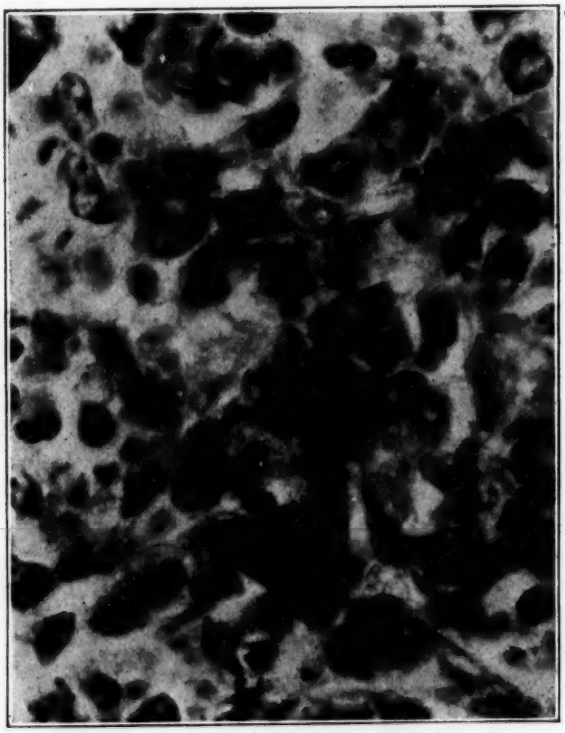

Fig. 17 (case 5).—Charcot-Leyden crystals at the periphery of the necrotic lesion. Iron hematoxylin stain.

Summary.—A 2 year old boy whose history indicates frequent asthmatic attacks was noted to have hepatomegaly, eosinophilia, leukocytosis and hyperglobulinemia, persisting for at least four months, but he did not have demonstrable pulmonary infiltration and had almost no symptoms during the period of study. Nodular disseminated lesions were demonstrated in the liver by means of a biopsy specimen.

The next case, included on clinical grounds, is of particular interest because of the absence of symptoms pointing to the respiratory tract, the onset with cutaneous and joint manifestations and the delay in hepatic enlargement.

CASE 6.—Wilmon J., a Negro boy, was admitted to the hospital in February 1949 at the age of 2 years because of painful swelling of the legs. In the past year he had had almost continuous colds, but cough had rarely been noted and no symptoms of asthma had ever been present. No drugs had been given. There had been no cutaneous eruptions. The child was brought up in Detroit and had received only pasteurized milk. He had not eaten pork. He had had no illnesses other than measles and chickenpox.

The mother was allergic to certain weeds in her back yard and after exposure regularly showed "hives."

The child's illness had begun three weeks before his admission, when he was suddenly unable to stand or walk and complained of pain in his legs. The knees were swollen and the child voluntarily stayed in bed. During the past ten days transient swelling of hands and toes had also been noticed. The swollen joints were tender, painful, warm and red. During the entire illness the child had been somewhat feverish. A fleeting pruritic rash described as hives was present over the face and chest during the last four to five days. Night sweats had been noted since the onset of the illness. There were no symptoms referable to the gastrointestinal tract.

Examination revealed a well nourished 2 year old boy in no apparent distress. The temperature was normal. The skin was clear. There was an abundant mucoid nasal discharge in which occasional eosinophils were seen on microscopic examination. The heart was of normal size and the sounds were of good quality, but there was a soft apical systolic murmur. The lungs appeared normal. The liver was not palpable at this time. No swelling, tenderness or deformity of the joints could be demonstrated.

Roentgenograms of the chest showed fairly prominent hilar and peribronchial infiltrations but no involvement of the pulmonary parenchyma proper. Films of the skeleton showed thickening of the cortex, in the opinion of the examiner of long standing, in the proximal and middle portions of both ulnas.

Cutaneous tests with Ascaris and Trichinella antigens gave negative reactions, as did the tuberculin patch test and the Mazzini test for syphilis. No sickling of red blood cells occurred in suitable preparations.

The hemoglobin concentration of the blood was 9.0 Gm., with 4,300,000 red blood cells and 50,100 white blood cells. The differential count showed 10 per cent neutrophils, 34 per cent lymphocytes and 51 per cent eosinophils.

Bone marrow aspiration revealed a definite increase in the number of eosinophil granulocytes.

Stool examinations failed to show parasites or ova. The remaining laboratory findings are included in tables 1 and 2.

Shortly after his admission the white blood cell count fell to 20,000 and the percentage of eosinophils to 9, but subsequently the eosinophils increased again to 36 per cent. After a short period of observation, the child was allowed to go home, since he was entirely free of symptoms of disease. He was seen again nine weeks later. At this time he had no complaints, other than recurrent coryza. Roentgenograms of the chest showed no change, but the white cell count was 31,000, with 52 per cent eosinophils. By now, interestingly enough, the liver had become enlarged and was palpable 2 fingerbreadths below the costal margin.

Summary.—A 2 year old Negro boy had a history of transient swellings, pain and tenderness of the joints of three weeks' duration and a shorter history of urticarious rashes. At the time of his admission no abnormal physical findings were present, but there was hyperleukocytosis and pronounced eosinophilia in the absence of demonstrable causes. These findings persisted during at least two months, at the end of which time hepatomegaly became apparent, although the clinical course had been asymptomatic, except for almost constant attacks of rhinitis.

Case 3 was an example of the combination of hepatic involvement with the typical features of the so-called Loeffler syndrome of eosinophilia and transient recurrent pulmonary infiltrations. In case 4, eosinophilia was present in the absence of clinical symptoms or demonstrable changes in either liver or lungs in the sibling of a child with the fully developed picture. Case 6 demonstrated the delay in hepatic enlargement following the development of eosinophilia and joint symptoms. These examples show the variability in the localization and the severity of what appears to be the same type of process. The next case seems to fit logically into this group as an illustration of a purely pulmonary localization and a classic example of the syndrome originally described by Loeffler.

CASE 7.—David M. was a white boy 3 years of age admitted to the hospital in October 1945 in coma, with a history of progressively severe vomiting of two weeks' duration. The past history was entirely noncontributory except for the fact that the child was known to have pica and to have eaten paint containing lead from the walls of his home on numerous occasions. There was no familial history of allergy. The findings on admission were characteristic of lead poisoning in a young child. The patient was in coma. There was weakness of the right leg. The liver was not palpable on this or any subsequent occasion. "Lead lines" were demonstrated in roentgenograms of the long bones. Moderate anemia was present, and basophilic stippling of the erythrocytes was noted in blood smears. Analysis of the urine showed a lead content of 0.6 mg. per liter as compared to the normal value of 0.04 mg. per liter.

In addition to these findings, roentgenograms of the chest showed an area of infiltration in the right upper pulmonary field which disappeared within twelve days. A month after his admission, however, new patchy shadows had appeared in both lungs, although there was no fever or cough and the physical examination failed to indicate consolidation. The reaction to the intradermal tuberculin test with increasing concentrations of old tuberculin up to 1:100 was negative.

Meanwhile, the initial white blood cell count had been 72,000, with 27 per cent eosinophils. The bone marrow likewise showed a definite increase in eosinophil granulocytes in the presence of an otherwise normal pattern. Both the total white cell count and the percentage of eosinophils fluctuated greatly but always both values remained strikingly elevated. At the time of his discharge from the hospital the white cell count was 49,200, with 82 per cent eosinophils.

The symptoms referable to lead poisoning meanwhile receded; the child recovered from his coma; the paralysis disappeared, and the child returned home on November 10.

The subsequent clinical course was satisfactory. Unfortunately, no further roentgenograms of the chest were made after December 7, when no change was demonstrated. At this time the white cell count was still 46,000 and 80 per cent eosinophils were counted. The child was next seen in September 1946. The anemia had disappeared. The white cell count was 13,800 and the eosinophils were still 19 per cent. In February 1947, the white cell count was 7,300 and the percentage of eosinophils had dropped to 15, but by August 1947, two years after the initial studies, it was still 12. On November 13, cutaneous tests with Ascaris and Trichinella antigens gave negative results. Repeated examinations of stool specimens failed to show the presence of ova or parasites. Other laboratory findings are given in tables 1 and 2.

The patient was then lost sight of and did not return until January 1949, when he was admitted because of a fracture sustained in an automobile accident. At this time no abnormal physical or roentgenologic findings were demonstrable. The hemoglobin concentration was 12.3 Gm., with 4,500,000 red blood cells and 10,400 white blood cells. The differential count showed 83 per cent neutrophils, 12 per cent lymphocytes, 3 per cent monocytes, 1 per cent basophils and 1 per cent eosinophils.

Summary.—In a 3 year old boy admitted with the typical picture of lead poisoning, pulmonary infiltrations, hyperleukocytosis and pronounced eosinophilia were noted as incidental findings. The pulmonary changes were variable and persisted for at least two months, while the eosinophilia, though less pronounced, remained present for at least two years but disappeared three years after the onset.

The last case, though less well studied than most of the preceding ones, is presented briefly because in this patient again a combination of chronic eosinophilia and hepatomegaly was encountered. In view of the previous observations, notably those in cases 4 and 6, the following case is interpreted as an example of a lesser degree of the same condition, especially as regards the leukocytosis and eosinophilia.

CASE 8.—Patricia P. was seen repeatedly in the clinic of this hospital because of febrile illnesses usually associated with cough, rhinitis or pharyngitis. On at least two occasions sulfadiazine had been given with apparent benefit. In August 1947, during one of her visits, enlargement of liver and spleen was noted and a hemogram at that time revealed moderately severe hypochromic anemia. The white blood cell count was then 11,400 and the eosinophils constituted 4 per cent of the total. There was no history of allergic symptoms in the patient or members of her family.

In September 1947, at the age of 2 9/12 years the child was admitted for the first time with complaints of fever and irritability. Physical examination disclosed no abnormal findings in regard to heart, lungs or abdominal organs. The nasal mucosa was congested and the tonsils were hypertrophied.

On her admission the white cell count was 8,800, with a differential count of 70 per cent polymorphonuclear leukocytes and 30 per cent lymphocytes. The hemoglobin concentration of the blood was 7.7 Gm., with 4,180,000 red blood cells. The Mazzini test gave a negative reaction. Roentgenograms of the chest revealed accentuation of the bronchovascular markings but no pulmonary consolidation.

Within three days after her admission a notable change in the blood picture occurred. The eosinophils rose to 19 per cent, although the total white cell count remained unchanged. Repeated stool examinations showed no ova or parasites.

The child was again given sulfadiazine and within twenty-four hours the fever had abated. A transfusion of whole blood was administered without reaction. At the end of a week the irritability had disappeared and twelve days after her admission the patient went home in an improved condition. The percentage of eosinophils two days earlier had been 21.

During the following year the child was seen repeatedly in the clinic and was doing well but the eosinophilia persisted. In September 1948, a year after the first admission, the liver was again palpable 3 fingerbreadths below the costal margin, and it was thought that the spleen was also enlarged. The white cell count was 8,800, with 16 per cent eosinophils. The hemoglobin concentration was 10.5 Gm. and red blood cells numbered 4,130,000.

During the following winter the patient had almost constant coryza and frequent cough but no serious illness. The liver remained palpable until December 1948 but could no longer be felt by February 1949. The eosinophilia decreased slightly, but, at the time of the last examination, there were 11 per cent eosinophils among 8,000 white blood cells. Nasal smears failed to show eosinophils. Trichinella cutaneous tests gave negative reactions. Numerous stool examinations were made in a vain attempt to demonstrate ova or parasites. The serum protein and globulin fractions were considerably elevated at this time.

Summary.—A 3 year old white girl whose only complaints were recurrent infections of the upper respiratory tract was observed to have recurrent enlargement of the liver, hyperglobulinemia and persistent increase in the number of eosinophils during a period of observation extending over eighteen months.

COMMENT

Pathologic Aspects.—From the appearance of the lesions studied in 4 of our patients, it is evident that the pathologic process is the same in each of the cases. The essential histopathologic features are those of focal necrosis, granuloma formation with histiocytes and giant cells and widespread eosinophilic infiltrations in the absence of demonstrable micro-organisms or parasites. The changes involve primarily the connective tissue framework of the portal tracts and in 1 instance a few of the venous structures. The arteries appear intact and the parenchyma is affected only secondarily, if at all. Healing takes place by a process of fibrosis, encapsulation and calcification.

Such variations as occur from case to case are readily explained by differences in the duration and severity of the process. This view is supported by the existence of fresh, necrotic, granulomatous and healed foci side by side in a single specimen, an observation which also clearly indicates the cyclic, recurrent nature of the pathologic process.

Lesions which appear to be identical with those described in our cases have been observed in the lung in the rare instances in which tissues from patients with the so-called Loeffler syndrome could be

studied pathologically.[8] In 2 of the cases reported by von Meyenburg [8a] eosinophilic infiltrations were seen in the portal tracts of the liver. This author also noted the presence of Charcot-Leyden crystals in some of the hepatic and pulmonary infiltrations but observed no focal destructive or granulomatous lesions in the liver. Involvement of the liver of the type and extent reported here seems to have been recorded only by Atmar,[6] in the case of a woman considered by the author to have familial eosinophilia, and by Perlingiero and György,[1] in a 2 year old child. The latter case, which the authors regarded as an allergic response to Ascaris infection, was remarkably similar to those observed by us, not only in its pathologic features but in its clinical, hematologic and biochemical aspects as well.

The Nature of the Lesions.—An allergic-hyperergic reaction has been assumed to be the basis of lesions such as we have described by virtually every one who has dealt with the subject. This point of view is strengthened by the frequent occurrence of frank clinical manifestations usually attributed to hypersensitivity, such as asthma, urticaria, purpura and swellings of the joints, in patients with Loeffler's syndrome of transitory pulmonary infiltrations and eosinophilia.[9] Furthermore, combination pictures have been described in patients with asthma-like clinical complaints in whom widely disseminated lesions of this type were accompanied with vascular changes of periarteritis nodosa and at times with frank rheumatic changes in the tissues.[10]

A process resulting from a state of tissue hypersensitivity is further suggested by the cyclic character of the tissue response, as indicated by the lesions in case 1 and by the widespread involvement of organs in the body; of the lungs and liver in case 3 and the liver and myocardium in case 2, of the liver and skin in case 5, of the joints, skin and liver in case 6, and possibly of the central nervous system in cases 1 and 2.

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8. (*a*) von Meyenburg, H.: Die pathologische Anatomie des "flüchtigen Lungeninfiltrates mit Blut-Eosinophilie," Virchows Arch. f. path. Anat. **309**:258, 1942. (*b*) Bayley, E. C.; Lindberg, D. O. N., and Baggenstoss, A. H.: Loeffler's Syndrome: Report of a Case with Pathologic Examination of the Lungs, Arch. Path. **40**:376 (Nov.-Dec.) 1945.

9. Hedvall, E.: Transitory Lung Infiltrations with Blood Eosinophilia, Acta tuberc. Scandinav. **16**:1, 1942.

10. (*a*) Meyer-Doerken, G.: Zur Frage der Sepsis mit allergischer Reaktion, Virchows Arch. f. path. Anat. **292**:374, 1934. (*b*) Roessle, R.: Zum Formenkreis der rheumatischen Gewebsveränderungen, mit besonderer Berücksichtigung der rheumatischen Gefässentzündungen, ibid. **288**:780, 1933. (*c*) Harkavy, J.: Vascular Allergy, J. Allergy **14**:507, 1943. (*d*) Bergstrand, H.: Morphological Equivalents in Polyarthritis Rheumatica, Periarteritis Nodosa, Transient Eosinophilic Infiltration of the Lung and Other Allergic Syndromes, J. Path. & Bact. **58**:399, 1946. (*e*) Smith, J. F.: Disseminated Focal Necrosis with Eosinophilia and Arteritis in a Case of Asthma (? Loeffler's Syndrome), ibid. **60**:489, 1948. Maier.[5b]

Negative evidence favoring a tissue reaction of hyperergic character may be seen in our failure to demonstrate micro-organisms or parasites in the lesions. Earlier investigators have likewise been unsuccessful in this respect, but to our knowledge studies including cultural methods and animal inoculations have rarely been made.

Localization.—It is apparent from a comparison of the individual cases that the same lesion in the liver may be present with or without demonstrable involvement of the lungs or other organs. If the view of the underlying condition as an allergic tissue response is correct, such variability in localization is to be expected. Indeed, the essential unity of the condition may be said to reside in the type of tissue response in which several organs may participate, and, as pointed out by Bergstrand [10d] and earlier by Roessle,[10b] the topographic classification of such a state may be almost impossible.

These considerations which obviously apply to periarteritis nodosa and the entire group of so-called collagen diseases are pertinent to our case material. In case 3 the patient had extensive pulmonary changes; several other patients had symptoms of asthmatic bronchitis but no demonstrable infiltrations, yet the hepatic lesions were identical. Moreover, the sister of the first child was entirely free of symptoms and neither lung nor liver could be shown to be involved by clinical methods, yet protracted eosinophilia of remarkable degree was present in this child and may logically be ascribed to the same underlying cause. On the other hand, no involvement of the liver was shown by clinical methods in the last of our patients, whose pulmonary lesions, blood picture and course of illness indicate the same process as that in the remainder of the group.

In the light of these observations, Loeffler's syndrome becomes a narrow band in the broad spectrum of sensitivity states in which the main "shock organ" happens to be the lung, while in our cases and in that of Perlingiero and György the liver was preeminently affected. On one side of this band may be found asymptomatic cases, such as our case 4, while the other side merges into the picture of more widespread organic involvement with irreversible vascular lesions, as in the cases described by Harkavy,[10c] Bergstrand [10d] and Smith.[10e]

If this concept of fluid transitions within a range of organic lesions secondary to hypersensitivity is difficult to fit into the framework of classic pathologic involvement, it is even more difficult to find a common denominator for clinical purposes of diagnosis and prognosis. For the clinician it is essential to know which organs or systems are involved and what the degree and character of the tissue changes may be in a given case. Eosinophilia of the blood alone is scarcely a criterion on which a clinical entity can be built, especially since the question will

always arise of what degree of eosinophilia should be considered significant, yet this feature seems to be about the only constant phenomenon among the variable and evanescent clinical manifestations. Pulmonary infiltrations may be lacking or may be so transitory as to escape notice, as shown by some of our cases and some of those reported by Bass [3a] and apparently belonging in the same group, as well as by Selander's case [2] published under the title eosinophilia leukemoides. Moreover, as Hedvall [9] pointed out, eosinophilia of the blood may precede the appearance of pulmonary shadows and persist following their resolution. Harkavy [10c] even mentioned the possibility that eosinophilic lesions may be present in the organs without accompanying eosinophilia of the blood.

Clinical Manifestations.—In spite of these limiting factors, it is obviously important to recognize cases of the sort described here and to differentiate them from leukemia, from irreversible hypersensitivity states, such as polyarteritis nodosa, and from the host of conditions said to be associated at times with eosinophilia. The small number of cases reported thus far, the scarcity of pathologic reports and the small size of our own series make such an undertaking appear premature. Our own experience and the frequency with which lesser but abnormal degrees of eosinophilia are seen in our clinic in patients in whom, as a rule, no thorough study is made lead us to believe that sufficient facts may be accumulated in a short time to delineate the clinical entity.

At this time, it is possible only to mention some of the features which, though inconstant, appear to be common and significant. We were struck with the age incidence in our patients, who ranged from 18 months—apparently the youngest patient described thus far—to 3 years old. This was also the age range of Selander's patient, the child studied by Perlingiero and György,[1] Becking's patient,[3b] Power's patient reported by Bass [3a] and 1 of the patients of Vallador, Mendoza and Pedrera.[11] The vast literature on Loeffler's syndrome shows, of course, that older children and young adults are commonly affected. It would seem, however, as though hepatic involvement were a feature commoner in early childhood than in later life, suggesting that the liver may function as the main "shock organ" in the younger patients. Apart from the case of Atmar, reported as familial eosinophilia but obviously, in view of the identity of the lesions, belonging in the same category as our cases, the vast literature on Loeffler's syndrome in adults contains scarcely any reference to hepatic enlargement or dysfunction.

11. Valledor, T.; Mendoza, R., and Pedrera, J.: Síndrome leucemoide eosinofílico, con imagen seudogranúlica pulmonar, de forma prolongada y evolución regresiva en la infancia, Bol. Soc. cubana de pediat. **11**:207, 1939.

By the same token hyperleukocytosis appears to be commoner and to reach higher degrees in children than in adults with this condition. The patient of Perlingiero and György had a maximum white blood cell count of 117,000; in one patient (case 2) of Bass 45,000 and in another (case 3) 50,000 leukocytes were counted and in Selander's patient 102,000. In our patients, such maximum counts as 105,000, 72,000 and 45,000 were observed.

Splenic enlargement has been described on a clinical basis in a number of patients, nearly all of them children. Our own experience leads us to suggest that in at least some of these patients the greatly enlarged left lobe of the liver may have been mistaken for the spleen.

The frequency of symptoms suggestive of allergic states, such as asthma, urticaria, angioneurotic edema, purpura and swellings of the joints, has been stressed by previous authors. It is clear, however, that such manifestations are far from constant. Cough, fever of low grade and recurrence of infections in the region of the paranasal sinuses and the upper respiratory tract are common, but many patients are free of symptoms even while roentgenograms may show extensive pulmonary lesions. This was true in the latter part of the course in our third patient.

Loeffler's original concept was based largely on the transitory character of both symptoms and pulmonary shadows. In the course of time this concept has undergone considerable modification, and it is now realized [12] that recurrent cyclic or prolonged monophasic cases may last for many months or even years.

The incidence of convulsive disorders seems rather high in our series, allowing even for the fact that in case 7 the encephalopathy was accounted for by lead poisoning. Selander's patient also had unexplained convulsions. The possibility of encephalopathy occurring as part of the syndrome on the basis of vascular sensitization is suggested, but a larger experience is needed for a definite statement.

Laboratory Findings.—The blood picture, apart from the variable but significant increase in eosinophil leukocytes and usually leukocytosis, is not characteristic. Modern anemia may be present, though not necessarily related to the condition. The thrombocytes are not affected and the picture should not be confused with that of chronic myelogenous leukemia in the absence of immature leukocytes. In one of our patients basophil leukocytes were also somewhat increased.

The bone marrow was studied in 5 of our patients and showed only a large but orderly increase in the number of eosinophil granulocytes.

Among other laboratory findings the increased erythrocyte sedimentation rate and the large increase in the plasma globulin fraction may

12. Kartagener, M.: Das chronische Lungeninfiltrat mit Bluteosinophilie, Schweiz. med. Wchnschr. **72**:862, 1942.

be mentioned. The latter findings was present in the patient of Perlingiero and György and in the 4 patients of our series in whom it was looked for. It is likely that the pronounced hyperglobulinemia and hyperproteinemia reflect the involvement of the liver in the allergic process. If this is true, such findings should prove of diagnostic value in the localization of the lesions.

The prognosis is said to be uniformly good in cases of Loeffler's syndrome. Von Meyenburg's pathologic studies were possible only because his patients died from accidents. Death seems to occur chiefly in patients with severe asthma and in those persons in whom the process merges into outspoken polyarteritis nodosa. Only 2 of the 10 children described in the reports collected by Selander died. Autopsies were rarely performed however, and death may have been due to unrelated complications. In the 1 patient of our group who died, the relationship between the condition indicated by the hepatic lesions, the encephalopathy and the fatal outcome is by no means clear.

Etiologic Considerations.—With regard to causation, a variety of agents have been incriminated, such as helminths, notably Ascaris, pollens, bacterial infections, including tuberculosis, and drugs.[13] Most authors have agreed that the mechanism through which all these factors affect the tissues is one of allergic nature. Von Meyenberg stated that it seems clear that a uniform etiologic basis must not be sought for but that a common pathogenetic principle exists. Our own observations regarding the causation are chiefly of negative value. In no instance were we able to demonstrate the presence of Ascaris in the lesions or elsewhere in the body, nor was there evidence of cutaneous sensitivity to the common parasitic antigens.

Wild and Loertscher[14] and others, including Perlingiero and György, incriminated Ascaris as an etiologic factor in their cases and cited in support the experiments of Koino and of Muller who were able to produce transient pulmonary shadows and moderate eosinophilia in man following the ingestion of large numbers of Ascaris eggs. It was pointed out by Wild and Loertscher, however, that these effects were short lived and that in order to explain the persistence of eosinophilia and of pulmonary shadows continuous reentry of larvae into the circulation would have to be postulated. Von Meyenburg and Bayley, Lindberg and Baggenstoss[8b] in their histologic studies were

13. Atwall, N.: Ein Beitrag zur Frage nach der Pathogenese, Aetiologie und Therapie der Eosinophilen Lungeninfiltrate, Acta med. Scandinav. **115**:350, 1943. Ham, J. C., and Zimdahl, W. T.: Loeffler's Syndrome and Pulmonary Infiltrations Accompanied by Peripheral Eosinophilia, Ann. Int. Med. **29**:488, 1948. Loeffler.[5a] Maier.[5b] von Meyenburg.[8a] Hedvall.[9]

14. Wild, O., and Loertscher, M.: Zur Aetiologie der flüchtigen Lungen-Infiltrierungen, Schweiz. med. Wchnschr. **64**:829, 1934.

unable to find larvae. Von Meyenburg stressed that these should be looked for in fresh preparations, as was done in 2 of our cases with negative results. In many cases of Loeffler's syndrome evidence of Ascaris infection or of other types of helminthiasis has been carefully looked for with negative results. While the presence of Ascaris or of ova in the stools is by no means conclusive evidence of a causal relationship, the possibility must be left open that in some instances this parasite is responsible for the syndrome. Our own observations give no support to this assumption.

In the cases reported by Engel,[15] sensitivity to pollens was demonstrated. Loeffler and his pupils likewise observed a seasonal incidence from May to August, suggesting pollen allergy. It is worth stressing, therefore, that our patients came to observation during the late fall and winter months.

Since 2 children had received sulfonamide drugs on many occasions, sensitivity to this group of drugs cannot be excluded, but in the remaining patients there was no history of drug ingestion at any time. The sterile character of the hepatic lesions was thoroughly established in case 5. There is nothing in our observations which would seem to conflict with the theory of an allergic-hyperergic nature of the condition, but we have no conclusive evidence as to the nature of the antigens.

Sensitivity to bacterial products is suggested by the history of innumerable infections in several of our patients. Without postulating a uniform etiologic basis for all cases of this type, we are inclined to regard sensitivity to bacteria or their products as the likeliest factor of causative significance in our group of patients. This view is based on the frequency of infections in the respiratory tract on one hand. On the other hand, the long persistence of the eosinophilia and the cyclic character of the pathologic process suggest a continued and recurrent pathologic stimulus. Chronic or recurrent infection could supply such a stimulus in a manner analogous to the role of recurrent streptococcic infections in rheumatic fever. The bacteriologic studies carried out in our patients, however, fail to point to any specific micro-organisms or unusual types of infection.

SUMMARY AND CONCLUSIONS

We present a group of cases characterized by eosinophilia of the blood and bone marrow, hyperleukocytosis and hyperglobulinemia persisting over long periods in young children ranging in age from 18 months to 3 years and presenting variable clinical pictures. Among

15. Engel, D.: Ueber eine eigenartige, anaphylaktische Erkrankung der Lunge, Beitr. z. Klin. d. Tuberk. **87**:239, 1935.

the manifestations were hepatomegaly, pulmonary infiltrations, asthmatic complaints, joint symptoms, urticaria and convulsions. Through much of their course, however, the majority of the patients were free of symptoms.

The essential unity of the conditions grouped together here is based on the character of the pathologic lesions demonstrated, by biopsy specimens or at autopsy, in the liver in 4 cases. The lesions consisted of necrosis, granuloma formation and severe eosinophilic infiltrations and corresponded to those described by other authors in the lungs of patients with the so-called Loeffler syndrome. They are interpreted as the expression of a common pathologic process of variable localization and severity, the nature of which is regarded as an allergic-hyperergic tissue response to undetermined antigens.

In contrast to the picture of Loeffler's syndrome in adults, with eosinophilia and leukocytosis of usually moderate degree and with predominantly pulmonary localization, the process in young children is likely to affect the liver and tends to be associated with a greater distortion in the blood picture. Loeffler's syndrome may be regarded as a special case of pulmonary involvement in a broad range of allergic phenomena. The clinical picture depends on the organs involved and on the severity of the process.

Further observations are needed to outline the entity, which appears to be common. Differentiation of these cases from leukemia is necessary. In general, the condition appears to be benign and self limited, though often of long duration.

5224 St. Antoine Street (2).

Dr. Louis M. Harley, Detroit, and Dr. Henri J. Breault, Windsor, Ontario, Canada, gave permission for study of their patients. The Research Laboratory of the Children's Fund of Michigan made the chemical and electrophoretic analyses of the serum proteins in cases 3 and 5.

RUBELLA-DEAFENED INFANTS

Comparison of a Group of Rubella-Deafened Children with a Group of Hereditarily Deaf Children and Their Sibs

LOUISE A. HOPKINS, M.S.
NORTHAMPTON, MASS.

With a Mathematical Appendix by Lydia Greene Kinzer, M.A., Columbus, Ohio

IN FEBRUARY 1946, a questionnaire entitled "Did You Have German Measles?"[1] appeared in the *Volta Review,* a periodical devoted to education of the deaf. Through the courtesy of Miss Josephine B. Timberlake, the editor, and Mrs. Laura Stovel, the assistant editor, I was able to have the replies to this questionnaire for analysis. However, I found that they were brief and I decided that a more detailed questionnaire would yield more valuable data, so I sent each of the mothers a second questionnaire to fill out for me. The mothers were most cooperative and eager to help. Not only

Dear Mrs.....:

The material which you sent to the Volta Bureau in answer to the questionnaire on German measles has been forwarded to me for analysis. I should be most grateful if you would answer the following questions so that I may have a little more information about your child and his history. Thank you so much for your help. I enclose a stamped, addressed envelope for your reply. May I have it as soon as possible?

Sincerely,
Louise A. Hopkins,
Research Department

Father's name? Date of birth?
Mother's maiden name? Date of birth?
Child's name? Date of birth?

HISTORY OF BIRTH

Normal birth? Instrumental delivery? Difficult labor?
Born at term? Number months premature? Length of labor?
Weight at birth? Number months overtime?
Were there any evidences of injury to baby at birth?
During which month of pregnancy did you have German measles?
Did you have any other illness during pregnancy? If so, what?
Was child breast fed? How long?
Was child bottle fed? How long?

HEALTH RECORD

Did child gain well and was health in general good?
Did child have any illnesses during infancy? If so, what?
When did child get first tooth? Did he have any convulsions?
When did child sit up alone? When did he walk alone?
Did he creep first? Were there any special difficulties?
Is child profoundly deaf? Is child partially deaf?
Has child ever had abscessed ears? Has child had mastoid operation?
Has child had cataracts? Both eyes? Left eye? Right eye?
Has child had heart trouble?
Is child mentally retarded as far as you know? Has he any other defects?
Has child any brothers and sisters? If so, please list names and ages on back of sheet, also specify whether any are deaf or hard of hearing.
Are there any other instances of deafness in either your family or your husband's family?
This information will be kept entirely confidential, so please answer in as much detail as possible.

From the Clarke School for the Deaf.

1. Tiffany, L.: Did You Have German Measles? Volta Rev. **48**:78 (Feb.) 1946.

TABLE 1.—*Data on Offspring of Mothers Who Had Rubella During First Month of Pregnancy*

Deaf Child									Normal Sibs					
Case No.	Sex	Place in Family	Weight at Birth Lb.	Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.	No. of Normal Sibs	Sex	Weight at Birth Lb.	Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.
1	F	1	5	1	7	11	16	0	..	..	..	..	..	..
2	M	1	3	14	17	19	24	0	..	..	..	..	..	..
3	F	1	5	3	16	7	15	0	..	..	..	..	..	..
4	F	1	4	0	13	12	19	0	..	..	..	..	..	..
5	F	1	4	2	11	8	16	0	..	..	..	..	..	..
6	F	1	5	4	10	8	15	0	..	..	..	..	..	..
7	F	1	5	13	8	8	14	0	..	..	..	..	..	..
8	F	1	5	11	14	12	24	0	..	..	..	..	..	..
9	F	1	6	0	13	8	19	0	..	..	..	..	..	..
10	M	1	6	8	12	7	13	0	..	..	..	..	..	..
11	M	1	4	11	11	12	24	1	F	7	14	10	6	11½
12	F	1	4	1	10	10	18	1	F	7	2	2 at 3 mo.	6	10
13	F	1	4	1	13	7	14	1	M	7	3	4	6	12
14	M	2	6	3	7½	5½	12	1	F	8	14	5	6	11

TABLE 2.—*Data on Offspring of Mothers Who Had Rubella During Second Month of Pregnancy*

Deaf Child									Normal Sibs					
Case No.	Sex	Place in Family	Weight at Birth Lb.	Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.	No. of Normal Sibs	Sex	Weight at Birth Lb.	Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.
15	M	1	4	0	10	8	17	0	..	..	..	..	..	..
16	F	1	6	5	15	10	25	0	..	..	..	..	..	..
17	F	1	5	15	7	6	14	0	..	..	..	..	..	..
18	M	1	5	13	8	7	14	0	..	..	..	..	..	..
19	M	1	6	8	..	..	12	0	..	..	..	..	..	..
20	M	1	6	0	11	6½	15	0	..	..	..	..	..	..
21	F	1	5	12	11	6	12	0	..	..	..	..	..	..
22	F	1	5	14	11	11	18	0	..	..	..	..	..	..
23	F	1	6	1	10	6	11	0	..	..	..	..	..	..
24	M	1	6	7	9 at 3	..	11	0	..	..	..	..	..	..
25	F	1	6	6	11	8	11	0	..	..	..	..	..	..
26	M	1	6	14	5	6	15	0	..	..	..	..	..	..
27	F	1	5	8	9	7½	13	0	..	..	..	..	..	..
28	M	1	5	10	..	..	12	0	..	..	..	..	..	..
29	F	1	4	12	11	6	15	0	..	..	..	..	..	..
30	F	1	3	4	9	10	18	0	..	..	..	..	..	..
31	F	1	5	0	8	7	16	0	..	..	..	..	..	..
32	F	1	5	6	10	5	11	0	..	..	..	..	..	..
33	F	1	4	2	11	11	28	0	..	..	..	..	..	..
34	M	1	5	4	11	6	11	1	F	9	6	..	6	..
35	F	1	4	9	6	6½	14	1	M	9	5	5	6	11
36	M	2	4	14	11	9	24	1	F	7	8	7	8	14
37	F	1	5	2	8	4	20	1	M	7	2	4	4	13
38	M	1	3	13	8	7	21	1	M	8	5	8	4	13
39	F	1	4	7	12	10	16	1	M	7	11	7	6	11
40	F	1	5	0	7	9	24	1	M	6	12	7	7	9
41	F	2	5	4	8	5	11	1	F	7	8	8	4	8
42	F	2	4	7	12	12	24	1	F	7	4	Died at 5 mo. of cardiac disorder		
43	F	2	5	4	9	12	Spastic	1	F	5	13	6	8	14
44	F	1	5	1	15	5	14	1	F	7	4	9	5	10
45	M	2	5	2	7	8	22	1	M	7	1	5	4½	14
46	F	1	4	9	6	7	12	1	M	7	1	8	7	12
47	M	2	7	8	4	6	11	1	F	9	0	6	7	12
48	F	1	6	3	13	9	24	1	F	7	2	9	5	10
49	F	1	7	8	8	8	14	1	F	8	2	5	5	12
50	M	1	6	4	11	8	15	1	M	7	8	6	7	13
51	M	1	7	12	8	7	12	1	M	9	8	4	6	12
52	M	1	8	0	7	6	14	1	M	8	12	5½	5	14
53	M	2	6	1	7	6½	11	1	M	6	1	6	7	12
54	F	3	5	15	14	6	12	2	M	9	3	14	3½	10
									F	9	12	10	4	12
55	F	2	6	7	6	5	14	2	F	6	1	..	5	12
									M	6	7	..	4	10
56	F	2	5	4	14	12	19	2	F	8	4	8	7	12
									F	7	8	9	6½	14
57	F	1	4	12	12	24	36	2	F	7	0	8	6	16
									F	6	8	9	7	14
58	M	3	6	6	9	8	16	3	M	8	0	..	..	..
									M	8	3	..	..	..
									M	8	0	..	..	..

did they fill out and return the second questionnaire promptly, but many of them also wrote me letters about their children and sent me names of other mothers they knew with "rubella children" who were

TABLE 3.—*Data on Offspring of Mothers Who Had Rubella During Third Month of Pregnancy*

	Deaf Child							Normal Sibs					
Case No.	Sex	Place in Family	Weight at Birth Lb.	Weight at Birth Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.	No. of Normal Sibs	Sex	Weight at Birth Lb.	Weight at Birth Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.
59	M	1	4	6	8	7	14	0	..	..	..	..	..	..
60	M	1	6	8	8	6	11	0	..	..	..	..	..	..
61	M	1	6	8	10	5½	10	0	..	..	..	..	..	..
62	F	1	7	0	7	6	14	0	..	..	..	..	..	..
63	F	1	6	2	10	7	15	0	..	..	..	..	..	..
64	F	1	6	2	9	11	17	0	..	..	..	..	..	..
65	M	1	7	4	6	7	13	0	..	..	..	..	..	..
66	F	1	6	4	8	7	13	0	..	..	..	..	..	..
67	M	1	7	0	9	8	14	0	..	..	..	..	..	..
68	M	1	6	1	9	16	Spastic	0	..	..	..	..	..	..
69	F	1	5	14	7	7	22	0	..	..	..	..	..	..
70	F	1	5	14	8	5	13	0	..	..	..	..	..	..
71	M	1	4	14	13	7	15	1	M	6	7	8½	5	11
72	F	1	5	1	9	9	18	1	F	9	10	4	8	12
73	M	1	7	13	6	9	14	1	F	8	4	6	3	8½
74	M	1	5	13	11½	8	19	1	M	8	2	6½	7	11½
75	M	1	6	12	9	5	12	1	M	7	0	5	7	11
76	M	1	5	8	8	6	19	1	M	7	8	6	6	13
77	M	1	8	5	6	6	13	1	F	8	3	6	6	13
78	F	1	8	4	7	6	12	1	F	8	4	8	6	13
79	F	1	7	2	10	9	12	1	F	..	..	..	..	..
80	F	2	7	4	6	9	19	1	F	7	3	8	6	15
81	F	3	5	4	10	7	10	2	M	7	0	6	6	9
									M	8	0	5½	5	9
82	F	1	5	0	9	9	17	2	F	7	1	5	7	12
									F	6	13	7	7	13
83	M	3	7	2	7	7	11	2	M	8	9	7	7	14
									M	8	6	8	6	12
84	M	3	6	0	11	8	15	2	M	6	12	8	12	15
									F	7	12	5	8	15
85	F	2	6	5	4	6	9	2	F	8	0	4	9	10
									F	7	0	4	9	11
86	M	1	6	10	8	6	11	2	M	7	7	8	6	13
									M	6	0	7	6	12
87	M	1	5	0	8	12	24	2	F	7	4	5	6	11
									F	7	4	8	8	13
88	F	2	6	0	11	6½	16	3	F	7	8	7	7	15
									F	7	0	6	6	12
									M	6	10	7	6	12
89	F	2	6	13	7	7	13	3	M	6	3	6	6	12
									M	7	4	6	5	11½
									M	7	4	6½	6	13
90	M	3	6	7	8	10	17	4	F	9	0	6	5	9
									M	9	0	6	8	12
									M	5	3	7	10	14
									F	5	8	7	10	15
									Twins					
91	F	5	5	0	5	6	11	4	F	7	0	5	6	12
									F	9	0	6	6	13
									M	7	0	6	5	12
									M	10	0	6	6	13
92	..	..	..	..	..	..	..	..	..	..	..	..	..	..

deaf. I obtained some names from the John Tracy Clinic, Los Angeles, and some from schools for the deaf. In all, I received information on a total of 92 cases in which the mother had rubella during the first, second or third month of a pregnancy which produced a deaf child.

TABLE 4.—*Data on Children with Hereditary Deafness*

	Deaf Child								Normal Sibs					
Case No.	Sex	Place in Family	Weight at Birth Lb.	Weight at Birth Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.	No. of Normal Sibs	Sex	Weight at Birth Lb.	Weight at Birth Oz.	Appearance of First Tooth, Age in Mo.	Sat Up, Age in Mo.	Walked, Age in Mo.
H 1	M	1	7	8	7	7	15	0	..	..	..	..	..	..
H 2	F	1	7	12	6	..	13½	0	..	..	..	..	..	..
H 3	M	1	7	4	5	6	10	0	..	..	..	..	..	..
H 4	F	1	6	14	6	..	12	0	..	..	..	..	..	..
H 5	M	1	7	10	4½	..	13	0	..	..	..	..	..	..
H 6	M	1	6	12	..	..	14	0	..	..	..	..	..	..
H 7	F	1	8	8	6	8	12	0	..	..	..	..	..	..
H 8	M	1	5	6	9½	8	15	0	..	..	..	..	..	..
H 9	F	1	5	4	9	20	22	0	..	..	..	..	..	..
H10	F	1	8	1	6	..	15	0	..	..	..	..	..	..
H11	F	1	8	4	..	..	10	0	..	..	..	..	..	..
H12	F	1	6	4	7	..	12	0	..	..	..	..	..	..
H13	M	1	6	11	Late	..	10	0	..	..	..	..	..	..
H14	M	1	8	0	..	..	12	0	..	..	..	..	..	..
H15	M	1	6	4	Late	..	14	0	..	..	..	..	..	..
H16	M	1	6	5	8	..	16	0	..	..	..	..	..	..
H17	F	1	6	0	8½	..	10	0	..	..	..	..	..	..
H18	M	1	6	9	5	9	20	0	..	..	..	..	..	..
H19	F	1	5	11	11	3	14	0	..	..	..	..	..	..
H20	F	1	7	2	7	7	22	0	..	..	..	..	..	..
H21	F	1	6	7	6	8	15	0	..	..	..	..	..	..
H22	F	1	6	0	6	4½	12	0	..	..	..	..	..	..
H23	F	1	7	11	11½	7	12	0	..	..	..	..	..	..
H24	M	1	6	2	12	..	12	1	F	..	..	6	5	11
H25	M	1	6	2	8	8	15	1	M	7	12	6	5	10
H26	F	2	9	1	8	8	17	1	F	8	6	10	4	12
H27	F	2	5	13	9	..	21	1	F	7	6	6	5	12
H28	F	1	5	15	6	6½	11	1	F	6	0	10½	8	13½
H29	F	2	7	8	4	6	12	1	M	6	8	6	8	12
H30	F	1	7	3	11	..	10	1	M	7	15	6	..	12
H31	F	1	6	13	12	9	19	1	F	6	0	12	..	36
H32	F	2	5	8	8	..	14	1	M	7	11	7	..	13
H33	M	1	6	7	9	9	22	1	M	8	3	6	8	18
H34	F	1	6	4	6	..	11	1	M	8	8	9	4	12
H35	F	2	4	0	7	..	12	1	M	6	13	6½	..	12½
H36	M	1	5	7	8	..	13	1	F	5	7	6	..	12
H37	F	1	6	12	5	6	14	1	M	7	12	4	6	12
H38	F	1	9	4	..	..	8	1	M	8	4	4	4	9
H39	M	1	8	0	4	5	11	1	F	6	12½	6	8	13
H40	F	1	7	11	6	6	11	1	F	6	8	10	6	12
H41	F	2	6	4	6½	6½	14	1	M	6	12	6	6½	14
H42	F	1	6	2	5	..	13	1	F	7	3	4½	7	12
H43	M	Twin	3	2	6	14	18	1	M	3	10	9	10	24
H44	M	1	9	0	..	..	17	2	F	8	3	6	..	16
									M	7	14	6	..	16
H45	F	2	8	8	8	..	12	2	F	7	2	9	7½*	14
									M	7	15¾	8	..	15
H46	F	2	6	0	9	8	14	2	M	..	..	9	7	13
									F	..	..	8	6	12
H47	M	2	8	8	..	..	16	2	F	7	10	3*	5*	17
									M	8	10	..	..	16
H48	F	1	7	12	7	7	15	2	F	7	7	6	8	11
									F	7	9	7	6	10
H49	F	3	8	2	4	6	10	2	M	7	8	10	..	10
									M	8	2	11	..	10
H50	F	3	7	11	5½	..	24	2	F	7	1	7	6	17
									F	6	5	8	6	10
H51	M	1	7	8	13	..	18	2	F	8	0	6	9	15*
									F	8	4	7	9	..
H52	M	1	7	5	7	..	30	Twins	F	6	6	6	7	9
									F	5	12	6	7	9
H53	F	2	9	15	3	6	13	2	M	8	15	4	7	16
									M	9	5	5	6	13
H54	M	1	7	9	9	..	15	2	F	8	1	6	5	12
									F	8	2	6	6	12
H55	F	1	6	11	8	..	11	2	M	6	14	5	6	11
									M	7	2	6	5½	12
H56	M	2	8	0	4	9	19	2	M	7	0	4½	4	12
									F	8	0	4	3½	8
H57	F	1	7	8	7	6	12	2	M	8	9	6	7	12
									M	9	8	5	7	13
H58	M	2	8	0	5	8	13	2	M	11	0	3	6	13
									M	7	3	6	7	13
H59	F	2	7	6	7½	7	12	3	F	7	0	7	6	13
									M	8	6	7½	7	13
									F	8	1	7½	6	13
H60	F	3	1	15	9	..	18	3	M	6	2	8	..	10
									F	7	2	8	..	12
									F	4	8	10	..	14
H61	F	3	8	0	5	..	14	4	M	8	6	4	6	14
									F	9	0	6	6	15
									M	8	4	6	6	15
									M	8	0	5	6	16

* Age for second sibling not stated.

It seemed wise, if possible, to study a control group of children who were born deaf, but whose mothers had not had rubella during pregnancy. For this group, I chose cases from the population of the Clarke School for the Deaf in which the child was an only child or, if not an only child, the only deaf child in the family. I gathered 61 such cases. The children of both this group and the rubella-deafened group were then compared with their hearing brothers and sisters. The rubella-deafened group had 72 brothers and sisters; the hereditarily deaf group had 59 brothers and sisters.

My problem was to determine (1) whether rubella in the mother caused a developmental arrest in the child and (2) whether variation in the period at which the rubella occurred modified the extent of the arrest. This gave rise to the further question whether the arrested development was brought about because the virus infection had affected all development, including that of hearing, or whether the fact that the child was deaf slowed his development in general.

Tables 1, 2, 3 and 4 show data on each child in detail. It was not possible to get all facts about each child, but all obtainable facts are listed.

TABLE 5.—*Sex of Deaf Children*

	No. of Boys	No. of Girls	Total
Rubella-deafened children:			
Month of pregnancy in which mother had rubella			
First	4	10	14
Second	18	27	45
Third	17	16	33
Hereditarily deaf children	23	39	62

SEX DIFFERENCES

It is of interest to mention a report by Martin,[2] of London, England, that, following the rubella epidemic in 1939-1940, 85 children were born deaf. Of these, 55 were boys and 30, girls. Among the 85 deaf children, there was "History of rubella during first 4 months of pregnancy: Boys 11, girls 13—total 24." This was 28 per cent of her entire group of deaf children born in 1940-1941.

In my group of 92 rubella-deafened children, there were 39 boys and 53 girls.

PLACE IN FAMILY

Reese [3] stated:

> . . . Out of 35 cases in which sufficient records are available, the affected baby was the first child in 26 instances, and in three others it was the second child. This notably high incidence in the children of primiparae indicates that the epidemic [of "German measles" in Australia in 1940] affected younger people.

2. Martin, S. M.: Congenital Defects and Rubella, Brit. M. J. **1**:855 (June 16) 1945.

3. Reese, A. B.: Congenital Cataract and Other Anomalies Following German Measles in the Mother, Am. J. Ophth. **27**:483 (May) 1944.

In my group of 92 rubella-deafened babies, the affected baby was the first child in 70 instances, and in 15 other instances it was the second child. In my group of 62 hereditarily deaf children, the affected child was the first child in 43 instances, and in 14 other instances it was the second child.

TABLE 6.—*Place in Family of Deaf Children*

	First	Second	Third	Fourth	Fifth
Rubella-deafened children: Month of pregnancy in which mother had rubella					
First	13	1	..	..	..
Second	33	10	2	..	..
Third	24	4	4	..	1
Hereditarily deaf children	43	14	4	1	..

BIRTH HISTORY

In analyzing the birth history of these groups, I observed that, among the rubella-deafened babies, there were 78 normal births, 12 instrumental births, 2 breech presentations and no cesarean sections. Among the sibs of the rubella-deafened children, there were 64 normal births, 5 instrumental births, 1 breech presentation and no cesarean sections.

Among the hereditarily deaf group, there were 41 normal births, 18 instrumental births, 1 breech presentation and 2 cesarean sections. Among the sibs of the hereditarily deaf children, there were 40 normal births, 12 instrumental births, 1 breech presentation and 1 cesarean section.

TABLE 7.—*History of Birth*

	Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children			Hereditarily Deaf Children	Sibs of Hereditarily Deaf Children
	First	Second	Third	First	Second	Third		
Normal birth	12	41	25	4	26	34	41	40
Instrumental birth	2	3	7	0	3	2	18	12
Breech presentation	0	1	1	0	0	1	1	1
Cesarean section	0	0	0	0	0	0	2	1
Premature birth	3	7	4	0	0	5	7	1
Breast fed	7	22	19	2	16	17	26	23

According to the mothers, there were 14 premature births among the rubella-deafened group, 5 among the sibs of the rubella-deafened group, 7 among the hereditarily deaf group and 1 among the sibs of the hereditarily deaf group.

Among the rubella-deafened group, 48 children were breast fed for at least a few weeks, among the sibs of the rubella-deafened infants, 35, among the hereditarily deaf group, 26 and among the sibs of the hereditarily deaf group, 23.

Table 7 analyzes this history in a little more detail.

WEIGHT AT BIRTH

In analyzing the weights at birth of these children and their sibs, I found the average weights as follows:

	Average Weight	
	Lb.	Gm.
Rubella-deafened children: Month of pregnancy in which mother had rubella		
First	4.9	2,222.6
Second	5.5	2,494.8
Third	6.2	2,812.3
Sibs of rubella-deafened children	7.5	3,401.9
Hereditarily deaf children	6.9	3,129.8
Sibs of hereditarily deaf children	7.5	3,401.9

Omitting from both rubella-deafened and hereditarily deaf groups those families in which the deaf child was the only child in the family, and comparing each rubella-deafened group with its own group of sibs, I found the average weights as follows:

	Average Weight		Average Weight of Siblings	
	Lb.	Gm.	Lb.	Gm.
Rubella-deafened children: Month of pregnancy in which mother had rubella				
First	4.6	2,086.5	7.8	3,538.0
Second	5.5	2,494.8	7.6	3,447.3
Third	6.2	2,812.3	7.4	3,356.6
Hereditarily deaf children	6.9	3,129.8	7.4	3,356.6

Dividing the children in the rubella-deafened groups and the hereditarily deaf group according to place in family, I found the average weights as follows:

	First Place			Second Place			Third Place		
	No. Children	Average Weight		No. Children	Average Weight		No. Children	Average Weight	
		Lb.	Gm.		Lb.	Gm.		Lb.	Gm.
Rubella-deafened children: Month of pregnancy in which mother had rubella									
First	13	4.8	2,177.2	1	6.0	2,721.5	0	...	.....
Their sibs	1	9.0	4,082.3	3	7.3	3,311.2	0	...	.....
Second	33	5.5	2,494.8	10	5.5	2,494.8	2	6.3	2,957.6
Their sibs	11	7.4	3,356.6	16	7.9	3,583.4	3	6.4	2,903.0
Third	24	6.2	2,812.3	4	6.4	2,903.0	4	6.1	.....
Their sibs	8	7.4	3,356.6	16	7.8	3,538.0	7	6.8	3,084.4
Hereditarily deaf children	43	6.8	3,084.4	14	7.3	3,311.2	4	6.4	2,903.0
Their sibs	16	7.6	3,447.3	24	7.2	3,265.9	13	7.9	3,583.4

PREMATURITY

According to Davison,[4] "Prematurity includes not only those infants born prior to the 40th week (280th day) of gestation but also those who have a birth-weight less than 2,500 Gm. (5½ lb.)." Using this statement as a measure of prematurity, I determined the following percentages:

	Percentage of Prematurity
Rubella-deafened children: Month of pregnancy in which mother had rubella	
First	64.2
Second	44.4
Third	21.2
Sibs of rubella-deafened children	1.4
Hereditarily deaf children	6.5
Sibs of hereditarily deaf children	3.5

4. Davison, W. C.: The Compleat Pediatrician: Practical, Diagnostic, Therapeutic and Preventive Pediatrics, ed. 5, Durham, N. C., Duke University Press, 1946, sect. 242.

Omitting from both rubella-deafened and hereditarily deaf groups those families in which the deaf child was the only child in the family, and comparing each rubella-deafened group with its own group of sibs, I found the following percentages of prematurity:

	Percentage	Percentage of Their Siblings
Rubella-deafened children:		
Month of pregnancy in which mother had rubella		
First	75.0	0.0
Second	55.5	0.0
Third	28.5	2.7
Hereditarily deaf children	7.7	3.5

Martin [4a] in analyzing a group of 19 rubella-deafened babies made the following statement: " . . . the smallest [birth weight was] 3½ and 4½ lb. Fifteen had a birth weight of between 5 and 6½ lb. and 2 of 7½ lb."

TABLE 8.—*Weight at Birth*

Weight at Birth		Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children			Hereditarily Deaf Children, Total No. 61	Sibs of Hereditarily Deaf Children, Total No. 57
					First, 4	Second, 31	Third, 37		
Lb.	Gm.	First, Total No. 14	Second, Total No. 45	Third, Total No. 33	Total No. 72				
2	907.2	..	..	..	..	..	..	1	..
2½	1,134.0	..	..	..	..	..	..	..	..
3	1,360.8	..	1	..	..	..	..	1	..
3½	1,587.6	..	1	..	..	..	..	..	1
4	1,814.4	5	2	..	..	..	..	1	..
4½	2,041.2	1	6	1	..	..	..	..	1
5	2,268.0	3	10	6	..	..	1	1	..
5½	2,494.8	2	4	2	..	..	1	4	1
6	2,721.6	2	11	9	..	3	2	12	4
6½	2,948.4	1	5	6	..	3	4	8	4
7	3,175.1	..	1	6	2	7	12	5	12
7½	3,401.9	..	3	1	..	5	4	13	9
8	3,628.7	..	1	2	1	5	6	9	14
8½	3,855.5	..	..	..	..	2	2	3	6
9	4,082.3	..	..	..	1	2	3	3	3
9½	4,309.1	..	..	..	..	4	1	..	1
10	4,535.9	..	..	..	..	..	1	1	..
10½	4,762.7	..	..	..	..	..	..	..	..
11	4,989.5	..	..	..	..	..	..	..	1
Average weight		4.9	5.5	6.2		7.5		6.9	7.5

Table 8 shows the range of weights at birth in each group of the present study.

AGE AT APPEARANCE OF FIRST TOOTH

In analyzing the age at which these children got their first tooth, I calculated the average age as follows:

	Age, Mo.
Rubella-deafened children:	
Month of pregnancy in which mother had rubella	
First	11.6
Second	9.4
Third	8.2
Sibs of rubella-deafened children	6.6
Hereditarily deaf children	7.2
Sibs of hereditarily deaf children	6.7

4a. Martin, S. M.: Deaf Babies: Thirty-Five Per Cent Rubella Victims, Volta Rev. **48**:410 (July) 1946; Congenital Defects from German Measles. Lancet **1**:479 (March 30) 1946.

Taking 7 months as the normal average age for the appearance of the first tooth,[4] I found the following percentages had their first tooth later than average:

	Percentage
Rubella-deafened children:	
Month of pregnancy in which mother had rubella	
First	92.8
Second	73.8
Third	66.6
Sibs of rubella-deafened children	28.1
Hereditarily deaf children	40.7
Sibs of hereditarily deaf children	27.1

Omitting from both rubella-deafened and hereditarily deaf groups those families in which the deaf child was the only child in the family, and comparing each rubella-deafened group with its own group of sibs, I found the following averages:

	Age, Mo.	Age of Their Siblings, Mo.
Rubella-deafened children:		
Month of pregnancy in which mother had rubella		
First	10.5	5.5
Second	9.4	7.2
Third	8.1	6.3
Hereditarily deaf children	7.2	6.7

Again, I found the following percentage got their first tooth later than average:

	Percentage	Percentage of Their Siblings
Rubella-deafened children:		
Month of pregnancy in which mother had rubella		
First	100.0	25.0
Second	68.0	45.8
Third	61.9	16.6
Hereditarily deaf children	44.4	27.1

Further analysis is shown in table 9.

TABLE 9.—*Appearance of First Tooth*

Age at Which First Tooth Appeared, Mo.	Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children			Hereditarily Deaf Children, Total No. 54	Sibs of Hereditarily Deaf Children, Total No. 59
	First, Total No. 14	Second, Total No. 42	Third, Total No. 33	First, 4	Second, 24	Third, 36 Total No. 64		
2	..	..	..	..	..	..	..	..
3	..	1	..	1	..	..	1	2
4	..	..	1	1	2	3	4	5
5	..	2	1	1	3	5	6	6
6	..	3	4	..	5	13	13	22
7	1	5	5	..	3	9	8	8
8	2	7	8	..	5	5	8	5
9	..	4	7	..	4	1	7	4
10	2	3	5	1	1	..	1	4
11	2	9	..	..	..	..	2	2
12	1	3	1	..	..	..	3	1
13	3	1	1	..	..	..	1	..
14	1	2	..	..	1	..	..	..
15	..	2	..	..	..	..	..	..
16	1	..	..	..	..	..	..	..
17	1	..	..	..	..	..	..	..
18	..	..	..	..	..	..	..	..
Average age	11.6	9.4	8.2		6.6		7.2	6.7

AGE AT WALKING ALONE

In analyzing the time at which these children walked alone, I found the average age as follows:

	Age, Mo.
Rubella-deafened children:	
Month of pregnancy in which mother had rubella	
First	17.3
Second	16.2
Third	14.5
Sibs of rubella-deafened children	12.1
Hereditarily deaf children	14.5
Sibs of hereditarily deaf children	13.3
(This group included 1 child with mongolism. With exclusion of this child, the average age was	12.9)

Taking 14 months as the average age at which normal children walk,[5] I found the following percentage walked later than average:

	Percentage
Rubella-deafened children:	
Month of pregnancy in which mother had rubella	
First	71.4
Second	51.1
Third	40.6
Sibs of rubella-deafened children	8.9
Hereditarily deaf children	37.7
Sibs of hereditarily deaf children	2.3

Omitting from both rubella-deafened and hereditarily deaf groups those families in which the deaf child was the only child in the family, and comparing each rubella-deafened group with its own group of sibs, I found the following average ages:

	Age, Mo.	Age of Their Siblings, Mo.
Rubella-deafened children:		
Month of pregnancy in which mother had rubella		
First	17.0	11.2
Second	17.1	12.1
Third	14.6	12.0
Hereditarily deaf children	14.7	12.9

Again, I found that the following percentages walked later than average:

	Percentage	Percentage of Their Siblings
Rubella-deafened children:		
Month of pregnancy in which mother had rubella		
First	50.0	0
Second	54.1	3.8
Third	47.6	13.5
Hereditarily deaf children	39.4	23.7

Further analysis is shown in table 10.

HEARING DEFECTS

In table 11, I analyzed the various groups according to amount of hearing and obtained the following results:

In the rubella-deafened groups were 53 profoundly deaf children and 38 partially deaf children. In the hereditarily deaf group 41 children were profoundly deaf and 21 children were partially deaf. None of the sibs of either group were deaf.

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5. Rand, W.; Sweeny, M. E., and Vincent, E. L.: Growth and Development of the Young Child, ed. 4, Philadelphia, W. B. Saunders Company, 1946, p. 262. Davison.[4]

In the rubella-deafened groups 13 children had had abscessed ears and 4 of their sibs had had abscessed ears. Eleven children in the hereditarily deaf group and 14 of their sibs had had abscessed ears.

Table 11 shows the distribution.

TABLE 10.—*Age at Walking Alone*

Age at Which Child Walked Alone, Mo.	Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children			Hereditarily Deaf Children, Total No. 61	Sibs of Hereditarily Deaf Children, Total No. 59
	First, Total No. 14	Second, Total No. 43	Third, Total No. 32	First, 4	Second, 26	Third, 37		
				Total No. 67				
8	..	..	..	..	1	..	1	1
9	..	..	1	..	1	4	..	3
10	..	..	2	1	4	1	6	6
11	..	8	4	1	2	4	5	3
12	1	6	3	2	8	12	12	16
13	1	1	5	..	3	9	4	11
14	2	6	4	..	6	2	10	5
15	2	5	2	..	..	5	6	4
16	2	3	2	..	1	..	3	5
17	..	1	3	..	..	..	2	2
18	1	2	1	..	..	..	3	1
19	2	1	3	..	..	..	2	..
20	..	1	..	..	..	..	1	..
21	..	1	..	..	..	..	1	..
22	..	1	1	..	..	..	3	..
23	..	..	..	..	..	..	..	..
24	3	4	1	..	..	..	1	1
25	..	1	..	..	..	..	..	..
26	..	..	..	..	..	..	..	..
27	..	..	..	..	..	..	..	..
28	..	1	..	..	..	..	..	..
29	..	..	..	..	..	..	..	..
30	..	..	..	..	..	..	1	..
3 to 4 yr	..	1	..	..	..	..	..	1
Average age	17.3	16.2	14.5		12.1		14.5	13.3 or 12.9

TABLE 11.—*Hearing Defects*

	Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children	Hereditarily Deaf Children	Sibs of Hereditarily Deaf Children
	First	Second	Third			
Number profoundly deaf	9	27	17	0	41	0
Number partially deaf	5	18	15	0	21	0
Number with abscessed ears	3	7	3	0, 1, 3	11	14

DEFECTS OTHER THAN DEAFNESS

In analyzing the defects other than deafness observed in these children, I found a total of 10 deaf children, born of mothers with rubella during either the first or second month of pregnancy, who also had congenital ocular defects. Three children had cataracts on both eyes and 7 children on one eye. One child had retinitis pigmentosa and one was cross eyed. None of the children born of mothers having rubella during the third month of pregnancy had any reported ocular defects.

A total of 30 children, born of mothers who had rubella during the first three months of pregnancy, were reported also to have congenital heart conditions. Of these, 3 were reported as having patent ductus arteriosus, 4, "greatly enlarged heart" and the rest, "murmurs." It was not possible to obtain a more definite diagnosis, but certainly some of these "murmurs" were presumably patent ductus arteriosus. One mother who had reported a "murmur" wrote several months later to tell me that her child had just had an operation for patent ductus arteriosus. Many of the reports mentioned that the child had been "a difficult feeding problem, was extremely nervous, was a poor sleeper and was very small for his age."

Four children were mentally defective; 2 children had spastic paralysis; 2 children were in casts several months because of congenitally dislocated hips; 1 child had an umbilical hernia; 1 child had an obstruction in the penis; 1 had hypospadias, and 1 child had a pilonidal dimple. A number of children had several defects other than deafness. These cases are listed in detail in the tabulation.

Case No.

11 "Enlarged and leaky heart"; defects cataracts on both eyes; nystagmus; a large umbilical hernia; wore braces on his legs for 7 months (this child was reported to be of normal mentality)
92 Patent ductus arteriosus; cataracts on both eyes; hypospadias; reported to be of low grade mentality
8 "Enlarged heart"; cataracts on one eye
13 Patent ductus arteriosus; cataracts on one eye
33 "Heart murmur"; cataracts on both eyes; mentally defective
2 "Heart murmur"; cataracts on one eye; mentally defective
9 "Heart murmur"; cataracts on one eye
38 "Heart murmur"; cataracts on one eye
39 "Heart murmur"; cataracts on one eye
43 "Heart murmur"; spastic paralysis
50 "Heart murmur"; obstruction in the penis
63 "Heart murmur"; pilonidal dimple
16 Cataract on one eye

TABLE 12.—*Defects Other Than Deafness*

	Rubella-Deafened Children: Month of Pregnancy in Which Mother Had Rubella			Sibs of Rubella-Deafened Children, Total No. 72	Hereditarily Deaf Children, Total No. 61	Sibs of Hereditarily Deaf Children, Total No. 57
	First, Total No. 14	Second, Total No. 45	Third, Total No. 33			
Ocular Defects						
Cataracts						
Both eyes	1	2	0	0	0	0
One eye	4	3	0	0	0	0
Retinitis pigmentosa	0	1	0	0	0	0
Crossed eyes	0	1	0	0	0	0
Cardiac Defects						
"Murmurs"	6	14	3	2	0	0
"Enlarged heart"	3	1	0	1	0	0
Patent ductus arteriosus	1	1	1	0	0	0
Other Defects						
Mentally defective	1	3	0	0	13	1
Umbilical hernia	1	0	0	0	0	0
Pilonidal dimple	0	0	1	0	0	0
Obstruction in penis	0	1	0	0	0	0
Hypospadias	0	1	0	0	0	0
Spastic	0	1	1	0	0	0
Congenital dislocation of hips	1	1	0	0	0	0

In this last patient there was no reported heart condition, but she was small and between 1 and 2 years of age gained only 1½ pounds (676.4 Gm.), though during her first year she apparently gained an amount commensurate with her birth weight."

For a total of 53 children the only reported defect was deafness.

Several children were reported to have had poor teeth due to lack of calcium, but in each instance the mother reported that she, too, had soft teeth, so this condition could not be due in these cases to the rubella during pregnancy.

In table 12, these various defects are listed under the following headings: ocular defects, cardiac defects and other defects.

SUMMARY

In order to determine whether rubella in the mother causes a developmental arrest in the child and whether variation in the period at which the rubella occurs modifies the extent of the arrest, a group of 92 cases in which the mother had rubella during the first, second or third month of a pregnancy which produced a deaf child was studied in detail.

As a control group, children who were born deaf but whose mothers had not had rubella during pregnancy (61 cases), from the population of the Clarke School for the Deaf were used. Each of these 61 children was an only child, or, if not an only child, he was the only deaf child in the family. Both the rubella-deafened children and the hereditarily deaf children were then compared with their hearing brothers and sisters.

From the data obtained concerning these children, it seems that rubella in the mother during the first three months of pregnancy does cause a developmental arrest in the child and that variation in the period at which the rubella occurs does modify the extent of the arrest.

There is the further question whether the arrested development was brought about because of the virus infection which had affected all development, including that of hearing, or whether the fact that the child was deaf slowed his development in general.

The development of the children in the hereditarily deaf group was not quite so rapid as that of their sibs. However, the amount of difference was so slight that it does not seem to indicate that the amount of arrest in the development of the rubella-deafened children could be laid to their deafness, but rather that it must be due to the virus infection in the mother.

MATHEMATICAL APPENDIX

Method.—The first hypotheses concerning the children described in this paper are stated in the form

$$m_y = m_z$$

where y and z are normally distributed with means m_y and m_z and variance σ^2. To test the hypotheses, values of t are calculated using the form [6]

$$t = \bar{x}\sqrt{\frac{n_1 n_2 (n_1 + n_2 - 2)}{(n_1 + n_2) S_x^2}}$$

where n_1 and n_2 indicate the sample size, $\bar{x}$, the difference between sample means, and S_x^2, the pooled sum of squares of deviations from the sample means.

Tables 13, 14 and 15 contain the results of the calculations for the comparison of rubella-deafened babies, born of mothers who had rubella in the first, second and third months of pregnancy, respectively, with other groups as indicated. Table 16 contains the results of the calculations for a comparison of the normal sibs of the rubella-deafened babies with the normal sibs of the hereditarily deaf babies.

Other hypotheses tested are of the form

$$m_{(x_1 - y_1)} = 0$$

where $(x_1 - y_1)$ is normally distributed with variance σ^2. To test the hypotheses, values of t are calculated using the form [7]

$$t = \frac{\bar{x}\sqrt{n}}{s_{\bar{x}}}$$

where n is the sample size (number of pairs), $\bar{x}$ is the mean and $s_{\bar{x}}$ is the estimate of the standard deviation.

Table 17 contains the results of the calculations for a comparison of hereditarily deaf babies and their normal sibs. Table 18 contains the results of the calculations for a comparison of rubella-deafened babies and their normal sibs.

Results.—The results presented in tables 13, 14 and 15 tend to substantiate the conclusion that variation in the period at which the rubella occurs does modify the extent of the arrest. These tables also show some significant ($P \leqq 0.05$)[8] differences between the rubella-deafened and other groups.

The results presented in table 16 for comparison of the normal sibs of the rubella-deafened children and the normal sibs of the hereditarily deaf children show that the hypotheses of the form

$$m_y = m_z$$

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6. Snedecor, G. W.: Statistical Methods Applied to Experiments in Agriculture and Biology, ed. 4, Ames, Iowa, the Iowa State College Press, 1946, p. 82.

7. Snedecor,[6] ibid. p. 45.

8. The value for P indicates the probability of chance occurrence.

TABLE 13.—*Comparison of Rubella-Deafened Children Whose Mothers Had Rubella in First Month of Pregnancy with Other Groups*

	First Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Hereditarily Deaf Children	First Month Rubella-Deafened Children	Sibs of Second Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Sibs of Third Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Sibs of Hereditarily Deaf Children
Weight at Birth—Boys												
n*	4	17	4	17	4	23	4	16	4	19	4	30
m (ounces)	85.0	96.2	85.0	101.6	85.0	110.9	85.0	124.9	85.0	118.0	85.0	125.1
σ	17.2	19.1	17.2	16.5	17.2	20.2	17.2	16.5	17.2	17.8	17.2	20.4
t		1.05		5.52		2.37		4.16		3.31		3.85
P		0.40		0.01		0.05		0.01		0.01		0.01
Girls												
n	10	27	10	16	10	38	10	15	10	18	10	27
m (ounces)	78.8	85.4	78.8	99.3	78.8	110.9	78.8	122.2	78.8	122.3	78.8	114.5
σ	12.1	14.4	12.1	14.7	12.1	23.8	12.1	18.8	12.1	15.9	12.1	16.7
t		1.27		11.48		3.13		6.38		7.42		6.88
P		0.30		0.01		0.01		0.01		0.01		0.01
Age at Appearance of First Tooth—Boys												
n	4	14	4	17	4	17	4	12	4	19	4	30
m (months)	11.9	8.2	11.9	8.6	11.9	7.3	11.9	6.6	11.9	6.6	11.9	6.3
σ	3.3	2.4	3.3	1.7	3.3	2.6	3.3	2.8	3.3	1.0	3.3	1.7
t		2.37		2.72		2.88		3.02		5.60		5.22
P		0.05		0.01		0.01		0.01		0.01		0.01
Girls												
n	10	27	10	16	10	36	10	12	10	18	10	30
m (months)	11.5	10.1	11.5	7.9	11.5	7.1	11.5	7.8	11.5	5.9	11.5	7.1
σ	2.7	2.7	2.7	2.1	2.7	2.1	2.7	1.7	2.7	1.5	2.7	1.8
t		1.36		3.74		5.36		3.82		6.82		5.74
P		0.20		0.01		0.01		0.01		0.01		0.01
Age at Sitting Up—Boys												
n	4	14	4	17	4	10	4	13	4	19	4	22
m (months)	10.9	7.1	10.9	7.8	10.9	8.3	10.9	5.5	10.9	6.6	10.9	6.0
σ	5.2	0.1	5.2	2.1	5.2	2.4	5.2	1.2	5.2	1.7	5.2	2.4
t		2.51		1.52		1.19		5.13		2.83		2.86
P		0.05		0.20		0.30		0.01		0.01		0.01
Girls												
n	10	27	10	16	10	20	10	14	10	18	10	24
m (months)	9.1	8.2	9.1	7.3	9.1	7.3	9.1	6.0	9.1	6.8	9.1	6.3
σ	1.9	4.2	1.9	1.8	1.9	3.3	1.9	1.2	1.9	1.8	1.9	1.5
t		0.60		2.39		1.60		4.86		3.10		4.34
P		0.60		0.02		0.20		0.01		0.01		0.01
Age at Walking Alone—Boys												
n	4	17	4	16	4	23	4	13	4	19	4	31
m (months)	18.2	14.9	18.2	14.5	18.2	15.6	18.2	11.9	18.2	12.1	18.2	13.3
σ	5.9	4.0	5.9	3.7	5.9	4.3	5.9	1.9	5.9	1.9	5.9	2.7
t		1.33		0.62		1.69		5.50		3.61		2.79
P		0.20		0 60		0.20		0.01		0.01		0.01
Girls												
n	10	26	10	16	10	38	10	13	10	18	10	28
m (months)	17.0	17.2	17.0	14.4	17.0	13.8	17.0	12.5	17.0	12.4	17.0	13.3
σ	0.9	6.4	0.9	3.7	0.9	3.6	0.9	2.1	0.9	1.7	0.9	4.9
t		0.08		2.17		2.80		6.31		7.93		2.31
P		....		0.05		0.01		0.01		0.01		0.05

* n indicates number of children in sample, m, mean of sample in units indicated, σ, standard deviation, t, $\frac{\text{difference of two means}}{\text{standard error of difference}}$, and P, the possibility of

TABLE 14.—*Comparison of Rubella-Deafened Children Whose Mothers Had Rubella in Second Month*

* n indicates number of children in sample, m, mean of sample in units indicated, σ, standard deviation, t, ..., and P, the possibility of

TABLE 14.—*Comparison of Rubella-Deafened Children Whose Mothers Had Rubella in Second Month of Pregnancy with Other Groups*

	Second Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	Hereditarily Deaf Children	Second Month Rubella-Deafened Children	Sibs of First Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	Sibs of Third Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	Sibs of Hereditarily Deaf Children
Weight at Birth—Boys												
n*	17	4	17	17	17	23	17	1	17	19	17	30
m (ounces)	96.2	85.0	96.2	101.6	96.2	110.9	96.2	115.0	96.2	118.1	96.2	125.1
σ	19.1	17.2	19.1	16.5	19.1	20.2	19.1	0.0	19.1	17.8	19.1	20.4
t		1.05		2.79		2.18		0.96		3.55		4.76
P		0.40		0.01		0.05		0.40		0.01		0.01
Girls												
n	27	10	27	16	27	38	27	3	27	18	27	27
m (ounces)	85.4	78.8	85.4	99.3	85.4	110.9	85.4	127.3	85.4	122.3	85.4	114.5
σ	14.4	12.1	14.4	14.7	14.4	23.8	14.4	14.5	14.4	15.9	14.4	16.7
t		1.27		3.03		4.94		4.75		8.05		6.84
P		0.30		0.01		0.01		0.01		0.01		0.01
Age at Appearance of First Tooth—Boys												
n	14	4	14	17	14	17	14	1	14	19	14	30
m (months)	8.2	11.9	8.2	8.6	8.2	7.3	8.2	4.0	8.2	6.6	8.2	6.3
σ	2.4	3.3	2.4	1.7	2.4	2.6	2.4	0.0	2.4	1.0	2.4	1.7
t		2.37		0.53		0.98		0.55		2.66		3.02
P		0.05		0.60		0.40		0.60		0.01		0.01
Girls												
n	27	10	27	16	27	36	27	3	27	18	27	30
m (months)	10.1	11.5	10.1	7.9	10.1	7.1	10.1	6.0	10.1	5.9	10.1	7.1
σ	2.7	2.7	2.7	2.1	2.7	2.1	2.7	3.6	2.7	1.5	2.7	1.8
t		1.36		2.69		4.85		2.38		5.70		4.91
P		0.20		0.01		0.01		0.05		0.01		0.01
Age at Sitting Up—Boys												
n	14	4	14	17	14	10	14	1	14	19	14	22
m (months)	7.1	10.9	7.1	7.8	7.1	8.3	7.1	6.0	7.1	6.6	7.1	6.0
σ	0.1	5.2	0.1	2.9	0.1	2.4	0.1	0.0	0.1	1.7	0.1	2.4
t		2.51		0.98		1.72		0.12		0.96		1.54
P		0.05		0.40		0.10		....		0.40		0.20
Girls												
n	27	10	27	16	27	20	27	3	27	18	27	24
m (months)	8.2	9.1	8.2	7.3	8.2	7.3	8.2	6.0	8.2	6.8	8.2	6.3
σ	4.2	1.9	4.2	1.8	4.2	3.3	4.2	0.0	4.2	1.8	4.2	1.5
t		0.60		0.83		0.86		0.90		1.36		2.11
P		6.60		0.50		0.40		0.40		0.20		0.05
Age at Walking Alone—Boys												
n	17	4	17	16	17	23	17	1	17	19	17	31
m (months)	14.9	18.2	14.9	14.5	14.9	15.6	14.9	12.0	14.9	12.1	14.9	13.3
σ	4.0	5.9	4.0	3.7	4.0	4.3	4.0	0.0	4.0	1.9	4.0	2.7
t		1.33		0.30		0.51		0.70		2.76		1.64
P		0.20		0.80		0.70		0.50		0.01		0.10
Girls												
n	26	10	26	16	26	38	26	8	26	18	26	28
m (months)	17.2	17.0	17.2	14.4	17.2	13.8	17.2	10.8	17.2	12.4	17.2	13.2
σ	6.4	0.9	6.4	3.7	6.4	3.6	6.4	1.3	6.4	1.7	6.4	4.9
t		0.08		1.53		0.88		1.86		3.07		2.64
P		..		0.20		0.40		0.10		0.01		0.01

* For key to symbols, see footnote to table 13.

TABLE 15.—*Comparison of Rubella-Deafened Children Whose Mothers Had Rubella in Third Month of Pregnancy with Other Groups*

	Third Month Rubella-Deafened Children	First Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	Second Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	Hereditarily Deaf Children	Third Month Rubella-Deafened Children	Sibs of First Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	Sibs of Second Month Rubella-Deafened Children	Third Month Rubella-Deafened Children	Sibs of Hereditarily Deaf Children
Weight at Birth—Boys												
n*	17	4	17	17	17	23	17	1	17	16	17	30
m (ounces)	101.6	85.0	101.6	96.2	101.6	110.9	101.6	115.0	101.6	124.9	101.6	125.1
σ	16.5	17.22	16.5	19.1	16.5	20.2	16.5	0	16.5	16.5	16.5	20.4
t		5.52		2.79		1.56		0.78		4.05		1.28
P		0.01		0.01		0.20		0.50		0.01		0.20
Girls												
n	16	10	16	27	16	38	16	3	16	15	16	27
m (ounces)	99.3	78.8	99.3	85.4	99.3	110.9	99.3	127.3	99.3	122.2	99.3	114.5
σ	14.7	12.08	14.7	14.4	14.7	23.8	14.7	14.49	14.7	18.8	14.7	16.7
t		11.48		3.03		1.81		1.86		3.79		3.01
P		0.01		0.01		0.10		0.10		0.01		0.01
Age at Appearance of First Tooth—Boys												
n	17	4	17	14	17	17	17	1	17	12	17	30
m (months)	8.6	11.9	8.6	8.2	8.6	7.3	8.6	4.0	8.6	6.6	8.6	6.3
σ	1.7	3.31	1.7	2.4	1.7	2.6	1.7	3.6	1.7	2.8	1.7	1.7
t		2.72		0.53		1.37		2.54		2.32		1.37
P		0.01		0.60		0.20		0.05		0.05		0.20
Girls												
n	16	10	16	27	16	36	16	3	16	12	16	29
m (months)	7.9	11.5	7.9	10.1	7.9	7.1	7.9	6.0	7.9	7.8	7.9	7.1
σ	2.1	2.66	2.1	2.7	2.1	2.1	2.1	3.6	2.1	1.7	2.1	1.8
t		3.74		2.69		1.28		0.81		0.19		1.48
P		0.01		0.01		0.30		0.50		0.90		0.20
Age at Sitting Up—Boys												
n	17	4	17	14	17	10	17	1	17	13	17	22
m (months)	7.8	10.9	7.8	7.1	7.8	8.3	7.8	6.0	7.8	5.5	7.8	6.0
σ	2.9	5.21	2.9	1.0	2.9	2.4	2.9	0	2.9	1.2	2.9	2.4
t		1.52		0.98		0.41		0.62		2.80		2.16
P		0.20		0.40		0.70		0.60		0.01		0.05
Girls												
n	16	10	16	27	16	20	16	3	16	14	16	24
m (months)	7.3	9.1	7.3	8.2	7.3	7.3	7.3	6.0	7.3	6.0	7.3	6.3
σ	1.8	1.93	1.8	4.2	1.8	3.3	1.8	0	1.8	1.2	1.8	1.5
t		2.39		0.83		0.07		0.77		2.38		1.88
P		0.02		0.50		....		0.50		0.05		0.10
Age at Walking Alone—Boys												
n	16	4	16	17	16	23	16	1	16	13	16	31
m (months)	14.5	18.2	14 5	14.9	14.5	15.6	14.5	12.0	14.5	11.9	14.5	13.3
σ	3.7	5.92	3.7	4.0	3.7	4.3	3.7	0	3.7	1.9	3.7	2.7
t		1.53		0.30		0.85		1.82		2.33		1.28
P		0.20		0.80		0.40		0.10		0.05		0.20
Girls												
n	16	10	16	26	16	38	16	3	16	13	16	28
m (months)	14.4	17.0	14.4	17.2	14.4	13.8	14.4	10.8	14.4	12.5	14.4	13.3
σ	3.7	0.93	3.7	6.4	3.7	3.6	3.7	1.29	3.7	2.1	3.7	4.9
t		2.17		1.53		0.64		3.85		1.72		0.80
P		0.05		0.20		0.60		0.01		0.10		0.50

concerning age at walking alone for boys can be rejected. The tests do not show significant ($P \leqq 0.05$) differences between the two groups of sibs for weight at birth, age at appearance of first tooth or age at sitting up for either sex, or for age at walking alone in the case of girls.

Hypotheses of the form

$$^{m}(x_1 - y_1) = 0$$

TABLE 16.—*Comparison of Sibs of Rubella-Deafened Babies and Sibs of Hereditarily Deaf Babies*

	Weight at Birth		Age at Appearance of First Tooth		Age at Sitting Up		Age at Walking Alone	
	Sibs of Rubella-Deafened Children	Sibs of Hereditarily Deaf Children	Sibs of Rubella-Deafened Children	Sibs of Hereditarily Deaf Children	Sibs of Rubella-Deafened Children	Sibs of Hereditarily Deaf Children	Sibs of Rubella-Deafened Children	Sibs of Hereditarily Deaf Children
Boys								
n*	36	30	32	30	33	22	33	31
t	0.09		0.52		0.22		2.35	
P	0.90		0.60		0.90		0.02	
Girls								
n	36	27	33	29	35	24	34	28
t	1.41		1.23		0.72		1.13	
P	0.20		0.30		0.50		0.30	

* For key to symbols, see table 13.

TABLE 17.—*Comparison of Hereditarily Deaf Babies and Their Normal Sibs*

	Weight at Birth	Age at Appearance of First Tooth	Age at Sitting Up	Age at Walking Alone
Boys				
n*	7	5	5	7
t	0.96	0.38	3.88	0.97
P	0.40	0.80	0.02	0.40
Girls				
n	12	13	6	13
t	0.64	1.29	1.18	0.64
P	0.60	0.30	0.30	0.60

* For key to symbols, see table 13.

TABLE 18.—*Comparison of Rubella-Deafened Babies and Their Normal Sibs*

	Weight at Birth	Age at Appearance of First Tooth	Age at Sitting Up	Age at Walking Alone
Boys				
n*	15	14	14	14
t	5.02	5.28	1.21	3.14
P	0.01	0.01	0.30	0.01
Girls				
n	17	17	18	17
t	5.93	4.10	0.43	2.90
P	0.01	0.01	0.70	0.01

* For key to symbols, see table 13.

were tested for rubella-deafened babies and their normal sibs, where x_1 represents a measurement on a rubella-deafened child and y_1 represents

the same kind of measurement for the normal sib of the same sex. (In case the rubella-deafened child had more than one normal sib of the same sex, y_1 represents the average for the normal children.) The hypotheses (table 18) can be rejected for both boys and girls for weight at birth, age at appearance of first tooth and age at walking alone. The hypotheses cannot be rejected for age at sitting up, for either sex. These results tend to substantiate the conclusion that rubella in the mother during the first three months of pregnancy causes developmental arrest in the child.

Hypotheses of the form

$$m(x_1 - y_1) = 0$$

were also tested (table 17) for hereditarily deaf babies and their normal sibs. Only one hypothesis can be rejected, that concerning age at sitting up for boys. These results do not indicate differences between these two groups for weight at birth, age at appearance of first tooth and age at walking for either sex, or for age at sitting up in the case of girls.

Clarke School for the Deaf (Miss Hopkins).

Mathematics Department, Ohio State University (Mrs. Kinzer).

STREPTOMYCIN IN TREATMENT OF WHOOPING COUGH

LEWIS W. WANNAMAKER, M.D.
JEROME L. KOHN, M.D.
AND
MANFRED WEICHSEL, M.D.
NEW YORK

THE ESSENTIAL procedures in the treatment of whooping cough, which included the use of human hyperimmune serums, were discussed in previous papers.[1] It has been shown that Hemophilus pertussis, the etiologic agent of whooping cough, is sensitive to streptomycin in concentrations of from 1 to 3 micrograms in a cubic centimeter of medium and, therefore, the antibiotic substance might have some therapeutic value. Bradford and Day[2] showed that streptomycin favorably altered the course of murine pertussis. The present report deals with the observations on the effect of streptomycin in children ill with whooping cough treated at the Willard Parker Hospital.

MATERIAL AND PROCEDURES

Streptomycin was administered to 129 patients over a six month period, from April 1 through Sept. 30, 1947. One hundred of these were under 1 year of age. There were an additional 21 children under 1 year who received no streptomycin (table 1).

The patients were divided into three groups according to the method of administration of streptomycin. The streptomycin was administered by (1) intranasal drops, (2) aerosol mist and (3) intramuscular injection. A fourth group was not to be given any streptomycin. In severely ill patients, in all groups, we frequently found it impossible to follow our planned routine.

Streptomycin hydrochloride was used in most of our patients. A few of the more recent patients received the calcium chloride complex of streptomycin.[3] In all instances, the dosage was expressed in micrograms of streptomycin base.

From the Willard Parker Hospital, Department of Hospitals.

1. Kohn, J. L., and Fischer, A. E.: Management of Whooping Cough with Special Reference to Infants, Am. J. Dis. Child. **73**:663 (June) 1947. Kohn, J. L.; Rudel, G.; Weichsel, M.; Buxbaum, L.; Fischer, A. E.; Guinther, O. H., and Lodyjensky, C.: Hyperimmune Serums in the Treatment of Whooping Cough: Clinical Results, with Notes on Bacteriologic Studies and Cutaneous Tests, ibid. **74**:321 (Sept.) 1947.

2. Bradford, W. L., and Day, E.: Therapeutic Effects of Streptomycin in Experimental Murine Pertussis, Proc. Soc. Exper. Biol. & Med. **60**:324 (Dec.) 1945.

3. The streptomycin for this study was furnished by Merck & Co., Rahway, N. J.

Streptomycin Administered by the Intranasal Route.—The dosage of streptomycin was not scaled to age. Originally, the nose drops were administered in a concentration of 10,000 micrograms per cubic centimeter. This was soon increased to 20,000 and, finally, 40,000 micrograms per cubic centimeter, so that the majority of the patients in this group received the higher dosages. Streptomycin was diluted to the proper concentration with isotonic sodium chloride solution; the solution was drawn from the vial with a small, sterile syringe and needle. The syringe with the needle removed was used to instil the streptomycin solution into the nostrils. These precautions were considered necessary to prevent contamination of the solution with organisms which might be resistant to streptomycin. In order to clear the nose, moderate suction was applied to the nostrils. Five-tenths cubic centimeter was then introduced into each nostril three times daily. Depending on the severity of the illness and the response noted, treatment was continued for five to twenty-one days, with an over-all average of 8.5 days. The average total dosage was 0.85 Gm.

Streptomycin Administered by the Aerosol Route.—Regardless of age, the dosage of streptomycin was 50,000 micrograms in 1 cc. of solution three times daily, or a total of 0.15 Gm. per day. The duration of treatment ranged from three to

TABLE 1.—*Total Number of Children with Whooping Cough Who Were and Were Not Given Streptomycin*

Age, Mo.	Number Given Streptomycin	Number Not Given Streptomycin
0 to 3	36	3
3 to 6	33	5
6 to 9	20	5
9 to 12	11	8
Over 1 yr	29	10
Total	129	31

twenty-five days, with an average of eight days. The total dosage per child averaged 1.2 Gm.

Since, during the catarrhal stage, the trachea and bronchi often contained a sticky, tenacious secretion, aspiration of the posterior portion of the pharynx was performed before treatment was begun.

A plastic hood was then placed over the head of the infant. This hood could be used in infants to the age of 9 to 12 months. It had two openings in front and a plastic tube inlet in the rear which normally carried oxygen. There was an ice compartment on top of the hood.

A plastic vaponephrin® nebulizer containing the 50,000 micrograms of streptomycin in 1 cc. of isotonic sodium chloride solution was plugged into one of the openings in front of the hood. The other opening was not plugged. During treatment the oxygen inlet was lightly plugged with absorbent cotton.

With the oxygen regulator set at 80 per cent and the oxygen running at approximately 4 liters per minute through the nebulizer, a moderate stream of aerosol mist was produced. The oxygen content of the hood during treatment averaged 40 to 50 per cent, as measured with an electromagnetic oximeter. Twenty to thirty minutes was required for complete nebulization of the solution. At the end of the treatment 0.25 to 0.5 cc. of water was introduced into the nebulizer. Another five minutes or more of operation was necessary for this to be nebulized. With the

addition of the water it was assured that the patient had received all the streptomycin solution, and clogging of the nebulizer from drying of the solution was prevented.

Special care was taken to maintain the nebulizer in a horizontal position throughout the treatment. In order to prevent the infant from dislodging the nebulizer, it was often necessary to use a mummy restraint. It was found advisable to administer treatments soon after feeding or at such a time as infants were usually quiet enough not to object to the temporary restraints.

In older children the small hood was not practical. In these children the nebulizer was placed directly in the child's mouth, or, if this was not possible, it was held there by a nurse. A larger-sized hood is now available for the treatment of the older children.

Streptomycin Administered by Intramuscular Injection.—The dosage for infants under 3 months of age was 50,000 micrograms every three hours, and for those from 3 months to 1 year, 100,000 micrograms every three hours. Patients over 1 year of age received from 100,000 to 200,000 micrograms every three hours. The average duration of treatment was six days.

Condition on Admission and Subsequent Course.—Patients on admission were graded according to the severity of the disease: *A*, a child was considered to be mildly ill when the paroxysms were not accompanied with cyanosis and vomiting was not frequent. Such a child did not appear to be exhausted. *B*, those considered to be moderately ill had frequent paroxysms, moderate cyanosis and persistent vomiting, but no ascertainable serious complications. *C*, severely ill infants were those in whom the paroxysms were followed by prolonged prostration and apnea. These last patients often showed signs of extensive pulmonary involvement or symptoms of encephalopathy.

The condition of the patient during the course of treatment was considered to be (1) good, when the paroxysms and emesis were distinctly less within five days after the beginning of treatment with streptomycin; (2) unchanged, or (3) poor, when the condition became worse.

Time of Admission.—Because of the difficulty of establishing a diagnosis of whooping cough in young children before the occurrence of the typical paroxysm, only a small number were admitted to the hospital before the whoop was first noted (3.7 per cent). Most of the children were admitted during the first week of the whoop, and about 20 per cent at a later period. The majority of children came from families of low economic status. Few had received any active immunization.

All the patients were observed daily by one of us, and notations of these observations were made.

Nasopharyngeal Cultures.—Nasopharyngeal cultures were obtained from nearly every infant, on admission, forty-eight hours after the last injection of streptomycin and again just before discharge from the hospital. The cultures were taken early in the morning, before any treatment was given.

Determinations of streptomycin levels in the blood were done with a method similar to those used in penicillin determination.

The possible development of resistance of H. pertussis to streptomycin was determined in a few patients by the standard method.

If a child had a febrile episode due to a respiratory or otitic infection, sulfadiazine or penicillin was given in addition to the streptomycin.

RESULTS

Intranasal Drops.—Fifty-two children were treated by the intranasal route. Only 3 were considered to be seriously ill on admission. Improvement was noted in 38 and no improvement in 14 (table 2). There were no toxic symptoms and no local irritation that could be attributed to the instillation of streptomycin.

Aerosol.—In a person ill with whooping cough, H. pertussis can be cultured only from the respiratory tract. It is conceivable that the penetration of the aerosol mist might have some effect on the etiologic agent. Abramson,[4] Bryson and Grace [5] and others were of the opinion that the aerosol mist may penetrate as far as the smaller bronchioles and alveoli of the lung.

There were 35 patients treated with streptomycin by the aerosol method. On admission 27 were moderately and 6 severely ill. Eleven

TABLE 2.—*Results of Treatment of Children with Whooping Cough with Streptomycin Nose Drops*

Age Group, Mo.	Condition on Admission, Number of Patients			Subsequent Condition, Number of Patients				Total Number of Patients
	Mild	Moderate	Severe	Good	Unchanged	Poor	Died	
0 to 3	0	3	0	1	2	0	0	3
3 to 6	0	12	0	11	1	0	0	12
6 to 9	0	8	1	8	1	0	0	9
9 to 12	0	9	1	6	4	0	0	10
Over 1 yr	3	14	1	12	6	0	0	18
Total	3	46	3	38	14	0	0	52

required the continuous use of oxygen from three to twenty-five days, an average of eight days.

The subsequent condition was considered improved in 28 patients. In 7 it was considered unchanged. There were no deaths. It is of interest to note that all 20 of the patients under 3 months of age showed definite improvement (table 3).

Intramuscular Injection.—Twenty-six patients were treated in this group, 21 of whom were under 1 year of age. Eighteen were considered to be mildly ill and 7 severely ill on admission. Seven of the patients required continuous oxygen from two to eleven days, an average of six days.

The condition after treatment was considered to be satisfactory in 22 patients. There was 1 death (table 4). We believe that the whooping cough was not the primary cause of death in this patient.

4. Abramson, H. A.: Principles and Practice of Aerosol Therapy of the Lungs and Bronchi, Ann. Allergy **4**:440 (Nov.-Dec.) 1946.

5. Bryson, V., and Grace, E. J.: Aerosol Therapy of Respiratory Disease, New England J. Med. **237**:683 (Nov. 6) 1947.

Streptomycin by Combined Routes.—Streptomycin was given by more than one route to 16 patients. Twelve of these children were treated simultaneously with aerosol mist and intramuscular injection. Eight of these 12 were considered to be severely ill on admission. There was none mildly ill. Eleven of the 12 required continuous oxygen therapy for two to twenty-five days, an average of eight days. The subsequent course was considered to be satisfactory in 5 children, unchanged in 2 and poor in 5. Four of the latter group died and will be discussed subsequently (table 5).

TABLE 3.—*Results of Treatment of Children with Whooping Cough with Streptomycin in Aerosol Mist*

Age Group, Mo.	Condition on Admission, Number of Patients			Subsequent Condition, Number of Patients				Total Number of Patients
	Mild	Moderate	Severe	Good	Unchanged	Poor	Died	
0 to 3	2	13	5	20	0	0	0	20
3 to 6	0	8	0	6	2	0	0	8
6 to 9	0	3	1	1	3	0	0	4
9 to 12	0	0	0	0	0	0	0	0
Over 1 yr	0	3	0	1	2	0	0	3
Total	2	27	6	28	7	0	0	35

TABLE 4.—*Results of Treatment of Children with Whooping Cough with Intramuscular Injection of Streptomycin*

Age Group, Mo.	Condition on Admission, Number of Patients			Subsequent Condition, Number of Patients				Total Number of Patients
	Mild	Moderate	Severe	Good	Unchanged	Poor	Died	
0 to 3	0	4	3	7	0	0	0	7
3 to 6	1	4	3	6	2	0	0	8
6 to 9	0	4	1	5	0	0	0	5
9 to 12	0	1	0	1	0	0	0	1
Over 1 yr	0	3	2	3	1	0	1	5
Total	1	16	9	22	3	0	1	26

Two children were given intranasal drops and intramuscular injections. Two children were given drops intranasally and aerosol mist.

Streptomycin Plus Hyperimmune Serum.—Nine children received human hyperimmune serum in addition to the streptomycin. Eight of these were severely ill on admission. Five of this group died.

COMPLICATIONS

It is interesting to note the complications that occurred during or after streptomycin therapy. Pulmonary involvement was present in 11 patients before streptomycin therapy was instituted; in 2 pulmonary

involvement was observed while therapy was being carried on and in 4 after the cessation. Infection of the upper respiratory tract, which included acute otitis media, was noted infrequently after the therapy was discontinued. No abnormal neurologic manifestations were seen after therapy was discontinued.

RESULTS IN CHILDREN WHO RECEIVED NO STREPTOMYCIN

There were 31 patients during this period of study who received no streptomycin. Twenty-one of these were under 1 year of age. Only

TABLE 5.—*Results of Treatment of Children with Whooping Cough with Streptomycin, Combining the Aerosol Form with Intramuscular Injection*

Age Group, Mo.	Condition on Admission, Number of Patients			Subsequent Condition, Number of Patients				Total Number of Patients
	Mild	Moderate	Severe	Good	Unchanged	Poor	Died	
0 to 3	0	2	4	3	1	0	2	6
3 to 6	0	0	3	1	0	0	2	3
6 to 9	0	1	0	1	0	0	0	1
9 to 12	0	0	0	0	0	0	0	0
Over 1 yr	0	1	1	0	1	1	0	2
Total	0	4	8	5	2	1	4	12

TABLE 6.—*Course of Illness in Children with Whooping Cough When No Streptomycin Was Administered*

Age Group, Mo.	Condition on Admission, Number of Patients			Subsequent Condition, Number of Patients				Total Number of Patients
	Mild	Moderate	Severe	Good	Unchanged	Poor	Died	
0 to 3	2	1	0	2	1	0	0	3
3 to 6	1	4	0	2	0	2	1	5
6 to 9	2	2	1	3	0	2	0	5
9 to 12	3	4	1	5	2	1	0	8
Over 1 yr	0	10	0	3	5	2	0	10
Total	8	21	2	15	8	7	1	31

2 were seriously ill on admission. In the patients under 1 year, 13 were judged to have had a favorable course, with no change in 3, and 5 became worse. The 1 death in the latter group was not due to whooping cough (table 6). The child had congenital hydrocephalus.

In the older group, all were considered to be mildly ill on admission. On subsequent course, 3 of these children did well, 5 remained unchanged and 2 did poorly (see table 6).

We had the impression that the course of the illness was not as favorable as in those children who had been given streptomycin by aerosol mist or intramuscular injection.

FATALITIES

There were 6 deaths during the period of this study. One of these children had chronic idiopathic hydrocephalus and was only moderately ill with whooping cough. This patient received no streptomycin. The other 5 all received streptomycin. We obtained reports of necropsy examinations in 4 of the children. A short summary of their clinical course follows.

REPORT OF CASES

CASE 1.—I. O., a girl 27 days old, a premature twin, weighed 5 pounds and 4 ounces (2,381 Gm.). On her admission the child was in poor condition and had severe paroxysms which terminated in cyanosis and apnea. There was evidence of diffuse pulmonary involvement. The nasopharyngeal culture yielded H. pertussis. In addition to the routine treatment, the child was given hyperimmune serum and streptomycin by intramuscular injection and aerosol mist. The child died seven days after her admission.

Necropsy revealed extensive bronchopneumonia and atelectasis. There was no evidence of aspiration of food into the lungs. The brain showed no changes which could be attributed to anoxia.

CASE 2.—L. Q., a girl 5 months old, had been coughing for three weeks. On her admission to the hospital she was having moderately severe paroxysms. On examination there was evidence of diffuse pulmonary involvement. The child became worse. On the ninth day in the hospital neurologic symptoms were noted which persisted until death on the fifteenth day. The white blood cell count was 96,000, with 61 per cent lymphocytes. The serum calcium content was 5.4 mg. per hundred cubic centimeters. Nasopharyngeal culture was positive for H. pertussis. In addition to the routine treatment, the child received hyperimmune serum, penicillin and calcium intravenously and streptomycin by the intramuscular and aerosol methods.

Necropsy showed bilateral pneumonia and atelectasis. There was a large amount of mucoid secretion throughout the entire respiratory tract. The brain showed congestion and gliosis.

CASE 3.—A. C., a girl 2 months old, had been coughing for two weeks and had been febrile for the last three days. On her admission the child was having severe prolonged paroxysms and was lethargic. On examination there was evidence of consolidation in the upper lobe of the right lung. Examination of the spinal fluid showed no abnormality. Nasopharyngeal culture was negative for H. pertussis. Convulsions were noted on the ninth day in the hospital and continued until the child died on the fifteenth day. In addition to the routine therapy the child was given 100 cc. of hyperimmune serum and streptomycin by intramuscular and aerosol methods. There was no necropsy.

CASE 4.—M. C., a girl 6 months old, had a history of two weeks of cough and hyperpyrexia for three days. On her admission frequent prolonged paroxysms were noted. The respirations were frequent and labored. On examination there was evidence of extensive pulmonary involvement. Hyperreflexia was also noted. On the second day in the hospital the child had convulsions and died soon after. The spinal fluid showed no abnormality. Nasopharyngeal culture did

not yield H. pertussis. In addition to the routine treatment, the child received hyperimmune serum intramuscularly and streptomycin by the intramuscular and aerosol methods. There was no necropsy.

CASE 5.—J. B., a girl 8 years old, had been chronically ill for six months. There was a history of cough for one week. On her admission the child was extremely emaciated. The paroxysms were infrequent, and roentgenograms showed a few patches of consolidation near the right hilus. The heart was perhaps slightly enlarged. There was no fever. The pulse rate was 180 per minute. The patient gradually became worse. There were convulsions on the fifth day in the hospital, which recurred, and she died on the tenth day. Nasopharyngeal culture was negative for H. pertussis. The blood calcium level was low. In addition to routine treatment she received 100 cc. of hyperimmune serum, penicillin and streptomycin intramuscularly and calcium intravenously.

Necropsy revealed acute bronchitis with a few patches of pneumonic consolidation and atelectasis. The heart was not hypertrophied. There was some edema of the myocardium, with minimal mononuclear cells in the interstitial tissue. No rheumatic involvement was evident. The brain showed evidence of anoxic encephalopathy.

CASE 6.—G. P., a boy 6 months old, had a history of cough of two weeks' duration. On his admission the child was having moderate paroxysms. There was chronic hydrocephalus, spina bifida and paralysis of both lower extremities. The whooping cough was only moderately severe, and he had recovered from his infection after four weeks. The child died six weeks after his admission. The nasopharyngeal culture yielded H. pertussis.

Necropsy showed extensive hydrocephalus, spina bifida and chronic cystitis. The lungs showed no abnormalities.

NASOPHARYNGEAL CULTURES

Positive nasopharyngeal cultures were obtained in 67 patients (43 per cent). In 54, cultures were obtained before, during and after treatment. In 31 of these 54 patients, H. pertussis was grown from the nasopharynx following the completion of therapy. Eight of these were in patients who had received aerosol; 4 were among those treated by the intramuscular route; 17 were in the group who were given nose drops, and 2 were among those who were treated by combined routes. The nasopharyngeal cultures of 23 children became negative during the course of treatment. Thus, in the dosage used by us by the various routes, no conclusive evidence was obtained that streptomycin had any effect on the presence of H. pertussis in the nasopharynx.

LEVELS OF STREPTOMYCIN

Levels of streptomycin in the blood were biologically measured in 7 patients. Specimens were taken just prior to the time for the next dose. Patients receiving streptomycin intramuscularly had blood levels of from 2 to 3 micrograms per cubic centimeter. Aerosol-treated patients gave inconsistent blood levels ranging from less than 0.5 to 2 micrograms per cubic centimeter. Streptomycin nose drops produced negligible blood levels.

RESISTANCE OF H. PERTUSSIS TO STREPTOMYCIN

The rapid development of resistance to streptomycin by many organisms alerted us to the possibility of what might occur with H. pertussis. Twelve patients with positive nasopharyngeal cultures on admission were followed with repeated cultures. Sensitivity tests were made. A total of 30 cultures yielding the organism was obtained of these 12 patients. In 6 of these, the streptomycin was given intranasally, in 5 by aerosol inhalation and in 1 by intramuscular injection. In 5 patients H. pertussis was cultured before, during and after treatment. In no instance was there any indication of increased resistance to streptomycin. In 2 additional patients the organism was cultured before and during, but not after, treatment. There was no tendency to develop resistance in the colonies isolated from these 2 patients. In all instances,

TABLE 7.—*Course of Illness in Children Mildly Ill with Whooping Cough on Their Admission to the Hospital*

Therapy and Route	Total No. of Mildly Ill Patients	Subsequent Condition, Number of Patients			
		Good	Unchanged	Poor	Died
Streptomycin in aerosol mist	2	2	0	0	0
Streptomycin intramuscularly	1	1	0	0	0
Streptomycin nose drops	3	3	0	0	0
Streptomycin by combined routes	0	0	0	0	0
Total number of patients treated with streptomycin	6	6	0	0	0
Number of patients given no streptomycin	8	7	1	0	0
Total number of all patients	14	13	1	0	0

the H. pertussis bacilli remained morphologically unchanged and formed a typical colony and produced strong hemolysis on Bordet-Gengou medium.

EVALUATION OF THERAPY

Fourteen patients were mildly ill on admission. Six of these were treated with streptomycin. Thirteen did well (table 7). Noting the mildness of the illness on admission and the small number of patients in the group, one cannot draw the conclusion that the improvement was due to the streptomycin.

Twenty-nine patients were severely ill on admission. Streptomycin was given to 27, of whom 16 showed improvement. It should be noted that 8 children, including the 5 who died, received human hyperimmune serum in addition to the streptomycin (table 8). Although we note again that no conclusion can be drawn from such a small group, the results suggest that streptomycin has some therapeutic value.

One hundred and seventeen patients, comprising 72.5 per cent of all children observed, were moderately ill on admission. Ninety-six

were treated with streptomycin. The clinical course of the illness in the children who were given streptomycin by either aerosol mist or intramuscular injection was more favorable than in those who were treated with nose drops. The progress of children who were not given streptomycin was the least satisfactory (table 9). This moderately

TABLE 8.—*Course of Illness in Children Severely Ill with Whooping Cough on Their Admission to the Hospital*

Therapy and Route	Total No. of Severely Ill Patients	Total Patients Also Given Serum	Subsequent Condition, Number of Patients			
			Good	Unchanged	Poor	Died
Streptomycin in aerosol mist	6	1	5	1	0	0
Streptomycin intramuscularly	9	1	7	1	0	1*
Streptomycin nose drops	3	1	2	1	0	0
Streptomycin by combined routes †	9	5	2	1	2	4*
Totals	27	8	16	4	2	5
Number of patients given no streptomycin	2	1	1	1	0	0

* These patients had also received pertussis immune serum (human) N. N. R.
† One of the patients in this group received a combination of intramuscularly and intranasally administered streptomycin; the other 8 were given streptomycin in the aerosol form and intramuscularly.

TABLE 9.—*Course of Illness in Children Moderately Ill with Whooping Cough on Their Admission to the Hospital*

Therapy and Route	Total No. of Moderately Ill Patients	Subsequent Condition, Number of Patients			
		Good	Unchanged	Poor	Died
Streptomycin in aerosol mist	27	21	6	0	0
Streptomycin intramuscularly	16	14	2	0	0
Streptomycin nose drops	46	33	13	0	0
Streptomycin by combined routes	7*	5	2	0	0
Total number of patients treated with streptomycin	96	73	23	0	0
Number of patients given no streptomycin	21	7	6	7	1†
Total number of all patients	117	80	29	7	1

* Four of these received streptomycin by a combination of the aerosol and intramuscular routes; 2 were given streptomycin in aerosol mist and nose drops; 1 received streptomycin intramuscularly and intranasally.
† Death was probably due to causes other than those directly related to whooping cough.

ill group of children seems large enough to warrant drawing tentative conclusions as to the effectiveness of streptomycin administered by various routes.

Since we felt that streptomycin administered by aerosol mist or intramuscular injection favorably influenced the course of whooping cough, another group of children was treated, using both methods

simultaneously, and with increased dosage. This procedure seemed even more effective. We hope to report on the results in a subsequent paper.

SUMMARY AND CONCLUSIONS

Streptomycin was administered over a period of six months to 129 children ill with whooping cough. One hundred were under 1 year of age. Thirty-one additional children were not treated with streptomycin.

The streptomycin was administered by nose drops, by aerosol mist and by intramuscular injection. There were no manifestations of toxicity due to the substance.

Cultures of material taken from the nasopharynx gave no evidence that the administration of streptomycin in the dosage and by the methods described had any effect on the presence of Hemophilus pertussis.

We had the impression that streptomycin when administered by aerosol mist or intramuscular injection favorably influenced the course of whooping cough, but that when given intranasally it had little therapeutic value.

It is difficult to compare the effects of various therapeutic agents on an illness such as whooping cough, in which the course varies widely in different persons. It is our opinion, however, that streptomycin used as here described was not as effective in the treatment of whooping cough as human hyperimmune serum.

Determination of streptomycin levels were made by Mrs. Carolyn Falk and of H. pertussis resistance to streptomycin by Miss Lucy Mishulu, of the laboratories of the New York City Department of Health.

50 West Ninety-Sixth Street.

FURTHER STUDIES ON USE OF STREPTOMYCIN IN TREATMENT OF WHOOPING COUGH

KENNETH S. SHEPARD, M.D.
DURHAM, N. C.
JEROME L. KOHN, M.D.
NEW YORK
SEYMOUR R. KAPLAN, M.D.
MIAMI BEACH, FLA.
AND
THEODORE C. ALLEN, M.D.
NEW YORK

IN A PREVIOUS study [1] observations were made on the course of whooping cough in a group of children, most of whom were under 1 year of age. Streptomycin was administered intranasally, by aerosol method or by intramuscular injection. We had the impression that the course of whooping cough was favorably influenced when streptomycin was given by either the aerosol method or intramuscular injection. Intranasal instillation seemed to have no therapeutic value.

This report concerns the treatment with streptomycin of a second group of infants and a group of older children.

MATERIAL AND PROCEDURES

This report deals with the observation of 64 patients from January to September 1948. The patients were divided into two groups according to age, those under 3 years and those over.

The younger group consisted of 43 children. A calcium complex of streptomycin [2] was administered over a five day period simultaneously by the aerosol route and intramuscular injection. In infants under 9 months of age the aerosol was administered under a plastic hood using the method previously described. In children from 9 months to 3 years of age the aerosol was administered by means of a cone made from a discarded roentgen film. The cone was placed over the child's nose and mouth. A few children had the nebulizer placed directly in the mouth. Suction was applied to the posterior portion of the pharynx before treatment was begun.

From the Willard Parker Hospital, Department of Hospitals, New York.

1. Wannamaker, L. W.; Kohn, J. L., and Weichsel, M.: Streptomycin in Treatment of Whooping Cough, Am. J. Dis. Child. this issue, p. 201.

2. The streptomycin for this study was furnished by Merck & Co., Rahway, N. J.

The solution which was put into a plastic nebulizer contained 50,000 micrograms of streptomycin per cubic centimeter. With the oxygen injector meter set at 80 per cent, and the oxygen running at approximately 4 liters per minute, a moderate stream of aerosol was produced through the nebulizer. After this solution was vaporized, 1 cc. of water was introduced into the nebulizer and the process was repeated. This aerosol treatment was given three times daily. In addition, these children were given 0.5 Gm. of streptomycin daily by intramuscular injection, equally divided into eight doses.

The second group consisted of 21 children over 3 years of age. The streptomycin was administered for five days by aerosol only, either through a cone or through the nebulizer placed directly in the child's mouth. The aerosol solution contained 0.33 Gm. of streptomycin in 2.5 cc. of isotonic sodium chloride solution. After nebulization, 2 cc. of water was introduced into the nebulizer and the process repeated. This aerosol treatment was given three times daily, a total dose of 1 Gm. a day.

TABLE 1.—*Results in Children with Whooping Cough Treated with Streptomycin by the Aerosol Route and Intramuscular Injection Simultaneously*

Route	Age Group	Condition on Admission			Subsequent Condition			Total No. of Patients
		Mild	Moderate	Severe	Good	Unchanged	Poor	
Aerosol and intramuscular, combined	1 to 6 mo.	..	7	11	15 *	2	1	18
	7 to 12 mo.	1	5	6	7 †	2	3	12
	1 to 3 yr.	1	6	6	7	..	6	13
Totals		2	18	23	29	4	10	43

* Two of these patients had relapses; both were severely ill on admission.
† One of these patients had a relapse and was severely ill on admission.

On their admission to the hospital patients were graded according to the severity of the disease as previously described: (*a*) those considered mildly ill had paroxysms, which were unaccompanied with cyanosis, and infrequent vomiting; (*b*) those considered to be moderately ill had frequent paroxysms, moderate cyanosis and frequent vomiting; (*c*) those considered severely ill had paroxysms which were followed by prolonged prostration and apnea.

The condition of the patient during the course of treatment was considered to be (*a*) good, when the paroxysms and emesis were distinctly less within five to seven days after the beginning of treatment with streptomycin; (*b*) unchanged, or (*c*) poor, when the illness became worse.

As noted in a previous study, most of the patients were admitted during the first week of the whoop.

Only 10 of the children were known to have had complete active immunization for whooping cough before the onset of illness.

None of the children were given any pertussis immune serum (human).

RESULTS

Group 1.—Combined Aerosol Route and Intramuscular Injection.—There were 43 children treated by the aerosol route and intramuscular injection simultaneously, of whom 30 were under 1 year of age. As

seen from table 1, the subsequent course of the illness was favorably influenced in most of the children under 1 year of age. The treatment was less effective in the children between 1 and 3 years. It should be noted that all who did poorly were severely ill on admission. Three children who improved after therapy had an increase of paroxysms from two to three weeks later.

Group 2.—Aerosol Route Only.—There were 20 children over 3 years of age treated by aerosol route only. One adult was also so treated. As seen from table 2, the subsequent course of the illness was favorably influenced in most of the children, but the results were not quite so good as in the youngest group.

TABLE 2.—*Results Obtained in Children Treated with Aerosol Only*

Route	Age Group	Condition on Admission			Subsequent Condition			Total No. of Patients
		Mild	Moderate	Severe	Good	Unchanged	Poor	
Aerosol	3 to 11 yr.	2	14	4	14 *	1	5	20
	Adult	..	..	1	1	..	..	1
Totals		2	14	5	15	1	5	21

* One of these patients had a relapse and was moderately ill on admission.

TABLE 3.—*Course of Illness in Children Moderately Ill on Admission to the Hospital*

Route	Age Group, Yr.	Total No. of Patients	Subsequent Condition		
			Good	Unchanged	Poor
Aerosol and intramuscular, combined	Under 1	12	9	2	1
	1 to 3	6	2	..	4
Aerosol	More than 3	14	10 *	1	3
Totals		32	21	3	8

* One of these patients had a relapse.

EVALUATION

There were only 4 children who were considered to be mildly ill on admission. All did well. Noting the small number, one cannot express any opinion as to the value of therapy.

There were 32 patients considered to be moderately ill on admission (see table 3). Eighteen under 3 years of age were treated simultaneously by the aerosol route and intramuscular injection. The remaining 14 children were treated by the aerosol route only. One child in the younger group who did well had a return of symptoms three weeks

later. Judging from this group, the results suggested that streptomycin had a favorable influence on the course of whooping cough.

There were 28 patients considered to be seriously ill on admission (see table 4). Twenty-three were under 3 years of age. Only 5 were older. It should be noted that 3 of the children who did well had a relapse from two to three weeks later. From table 4 one must conclude that the subsequent course in the seriously ill group was almost as favorable as in those moderately ill on admission.

COMMENT

We noted in the previous study that the use of streptomycin in whooping cough was encouraging with either the aerosol method or intramuscular administration in a group of children, most of whom were under 1 year of age. We felt, therefore, that by combining the

TABLE 4.—*Course of Illness in Children Severely Ill on Admission*

Route	Age Group, Yr.	Total No. of Patients	Subsequent Condition		
			Good	Unchanged	Poor
Aerosol and intramuscular, combined	Under 1	17	12*	2	3
	1 to 3	6	4	..	2
Aerosol	Over 3	5	3	..	2
Totals		28	19	2	7

* Three of these patients had relapses.

aerosol and intramuscular methods the resultant improvement might be further enhanced. However, there seemed to be no advantage in the combined treatment.

It is true that the administration of streptomycin seemed to have little effect on the course of illness in some children who were seriously ill on admission. By contrast, a number of infants who were critically ill on admission improved dramatically. Within five days the paroxysms were much less frequent and not as prolonged.

There were 2 instances in which 2 children in the same family were admitted together. One from each family was immediately treated with streptomycin and improved; whereas the other child showed no improvement until it, too, was so treated.

SUMMARY

Sixty-four of the children who were admitted with whooping cough during a period of eight months were treated with streptomycin. Thirty were under 1 year, 13 between 1 and 3 years and 21 over 3 years of age.

In the children under 3 years of age, the streptomycin was administered simultaneously by aerosol route and intramuscular injection. In children over 3 years of age the streptomycin was given by aerosol only.

We had the impression that streptomycin had a favorable influence on the course of whooping cough in children under 1 year of age. The clinical course was not quite so favorable in children over 1 year of age.

There seems to be no advantage in the combined administration of streptomycin by aerosol route and intramuscular injection when compared with either aerosol or intramuscular injection alone.

50 West Ninety-Sixth Street.

SPREAD OF DIARRHEA OF UNKNOWN ORIGIN IN A WARD FOR INFANTS

JOHN JUDD SHIELDS, M.D.
PHILADELPHIA

NUMEROUS epidemics of diarrhea of unknown origin have been reported from nurseries for the newborn in recent years. That a similar type of diarrhea may be hazardous in a hospital ward for infants has not been emphasized. Frant and Abramson [1] reported that no secondary cases occurred among older infants and children in open pediatric wards in which infants with epidemic diarrhea of the newborn were quartered. Rubenstein and Foley [2] likewise stated that no cases developed in older infants known to have been exposed to babies with epidemic diarrhea. Dodd,[3] however, observed that secondary infections occurred in infants up to at least 6 months of age, premature infants being severely affected. Clifford [4] noted the tendency of diarrhea to spread in pediatric wards after admission of babies from nurseries with epidemics, in contrast to the lack of spread when the infecting organism belonged to the Salmonella or dysentery group. McCluskey [5] mentioned an epidemic of diarrhea which occurred in the ward for infants of the Children's Hospital, of Pittsburgh, in March 1947, with 25 severe cases and 2 deaths. The experiences reported here tend to support the impression that so-called diarrhea of the newborn is not confined to the "newborn" period and is not readily controllable when introduced into a hospital ward for infants.

In the eighteen month period from Jan. 1, 1946 to June 30, 1947, there were two distinct outbreaks of diarrhea in the ward for infants of St. Christopher's Hospital for Children. During this time there were

From St. Christopher's Hospital for Children and the Department of Pediatrics, Temple University School of Medicine.

1. Frant, S., and Abramson, H.: Epidemic Diarrhea of the Newborn, in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1941, vol. 1, chap. 28, p. 19.

2. Rubenstein, A. D., and Foley, G. E.: Epidemic Diarrhea of the Newborn in Massachusetts, New England J. Med. **236**:87 (Jan. 16) 1947.

3. Dodd, K., in discussion on Infection in the Newborn Period, J. Pediat. **30**:696 (June) 1947.

4. Clifford, S.: Diarrhea of the Newborn, New England J. Med. **237**:969 (Dec. 25) 1947.

5. McCluskey, E. R., in discussion on Ritter, O'Connell and Lucente.[6]

95 cases of diarrhea in infants in the hospital, and it appeared likely that in 33 instances the diarrhea was acquired by cross infection within the hospital. Serious enteric infections acquired in the hospital had not previously been recorded. The only hospital infections which occurred with any significant frequency were those of the respiratory system, and the incidence of these appeared to be reduced after the installation of ultraviolet lamps over the entrances to the cubicles in the wards.

The principal portion of the ward for infants was divided into three sections, each of 8 cribs. Each crib was situated in an individual cubicle; the partitions between sections and between cubicles, however, did not extend from floor to ceiling. In addition, there were a separate but adjacent nursery for premature infants with 3 bassinets and an isolation room with 2 cribs. The building was modern, and a high standard of cleanliness was maintained.

The ordinary isolation procedures included the washing of hands before and after the handling of each infant; gowns and masks were not used routinely. During the outbreaks of diarrhea to be described, the infants with diarrhea were kept in one or two of the 8 crib sections, to which infants without diarrhea were not admitted. Gown technic was maintained for each infant, in addition to hand washing as described previously. Separate nurses were provided for the wards for infants with diarrhea, and the entrance of physicians, technicians and maids was limited as much as possible. Diapers and clothing of the infants were heat sterilized on removal from the ward. The bottles and nipples were washed in the ward and placed in boiling water for at least twenty minutes prior to their removal to the formula room. Subsequent washing and sterilization were then done in a space separated from the formula preparation area by a partition 4 feet (121.9 cm.) high. Exacting formula room technic was observed, but terminal sterilization of the formulas was not carried out.

All infants (under 2 years of age) admitted to the ward during the eighteen month period who had diarrhea of undetermined origin at the time of admission or who showed it prior to discharge from the hospital were included in the epidemiologic survey. Each infant was listed only once, although a few infants were readmitted for recurrence of diarrhea soon after discharge from the hospital.

Fourteen infants in the group were admitted to the ward with diarrhea associated with infection of the upper respiratory tract; these were older infants who recovered with a minimum of therapy. It is probable that some infants with mild attacks of parenteral diarrhea were omitted from the study because such a diagnosis was not listed on the discharge record form. One infant with enteritis due to a Salmonella organism was excluded from the series. In none of the infants in the study group was the origin of the diarrhea disclosed by routine cultures of the stools.

COURSE OF EPIDEMIC

In the early months of 1946, infants with diarrhea, most of them with concomitant infections of the upper respiratory tract, were sporadically admitted. All these infants recovered quickly and there was no evidence of cross infection.

On May 6, 1946, an infant 6 months of age was admitted with severe diarrhea which began April 21 on board a ship from England, and on May 20 an infant 10 weeks of age was admitted whose diarrhea started May 16 on a ship sailing from France. Epidemics of diarrhea

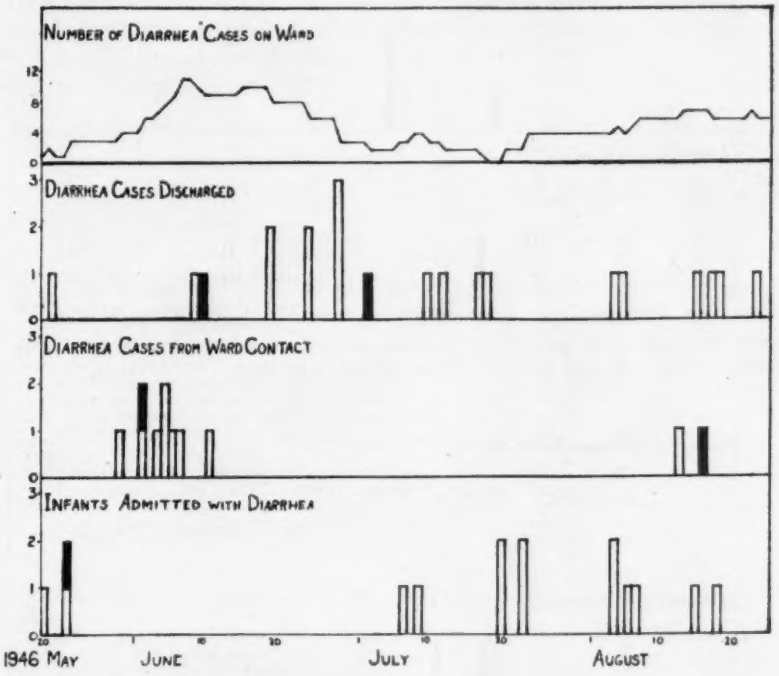

Fig. 1.—Course of spread of diarrhea in a ward for infants from May to August, 1946. Shaded blocks indicate infants who died.

were said to have occurred among the infants on these ships. These 2 infants were discharged as recovered on May 21 and June 9, respectively. On May 23, 2 other infants with severe diarrhea were admitted. On May 30, while the latter 3 infants were still in the ward, the first case in the hospital developed and was followed by 7 others within the next week (fig. 1). After this explosive start the epidemic subsided with only 1 additional case. The 9 infants involved ranged in age from 16 days to 15 months, 6 of them being 5 months or more of age.

During the remainder of 1946 (fig. 2), 8 infants in the ward had diarrhea without any well defined epidemic; only 1 of these was more

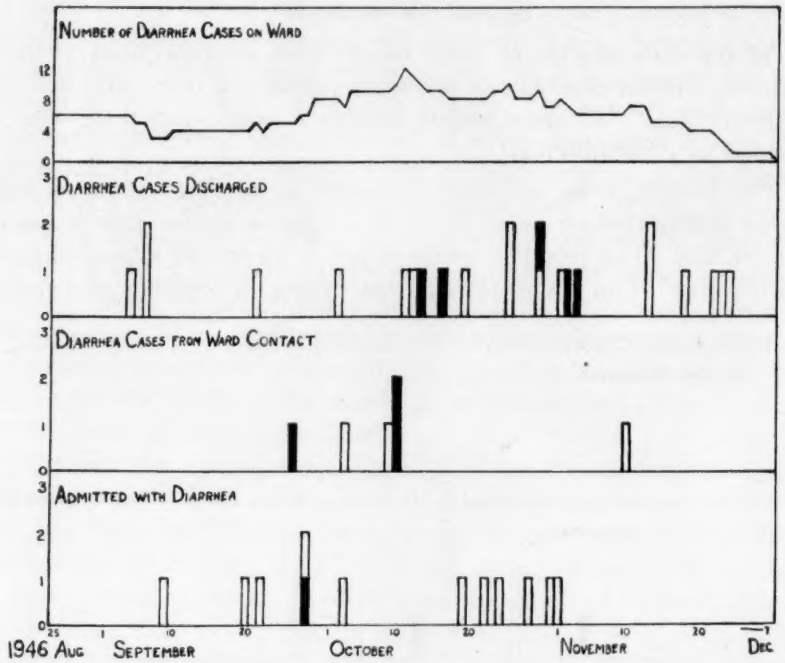

Fig. 2.—Course of spread of diarrhea in a ward for infants from August to December 1946. Shaded blocks indicate infants who died.

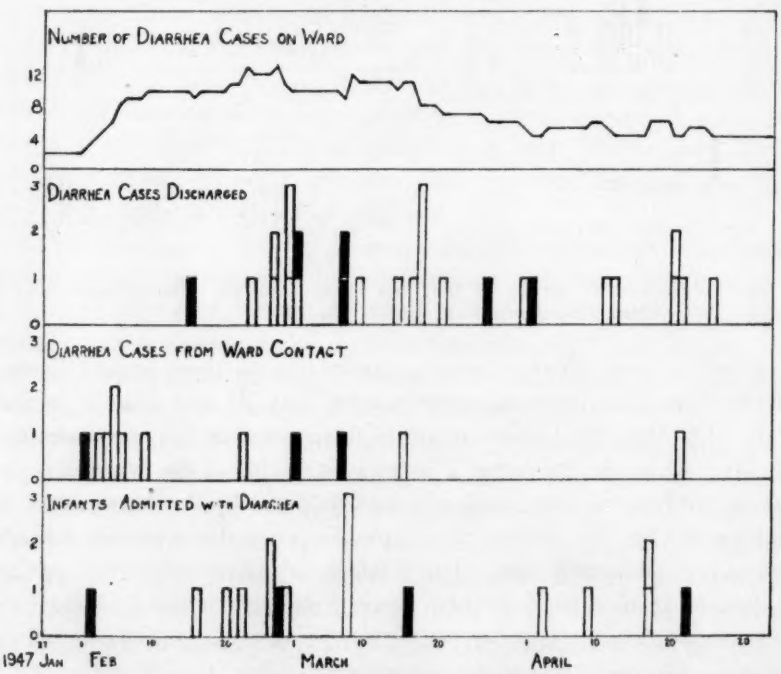

Fig. 3.—Course of spread of diarrhea in a ward for infants from January to April 1947. Shaded blocks indicate infants who died.

than 3 months of age. From Dec. 8, 1946 to Jan. 5, 1947, there were no cases of diarrhea on the ward.

Between Jan. 6 and Feb. 2, 1947, 5 infants with diarrhea were admitted, and there was another sudden outbreak of ward cross infection, with 7 contact cases occurring between February 1 and 9 (fig. 3). For the next six weeks, the census of infants with diarrhea averaged 10 as a result of the development of 4 new cases within the hospital and the admission of 10 infants with diarrhea. The peak incidence approximated the occurrence of the epidemic of diarrhea of the new-

TABLE 1.—*Summary of Cases of Diarrhea of Unknown Origin in Infants under Two Years of Age at St. Christopher's Hospital for Children, Jan. 1, 1946 through June 30, 1947*

	Total No. of Infants, 0 to 23 Mo. of Age	Age at Onset of Diarrhea (Inclusive)		
		0 to 3 Mo.	4 to 11 Mo.	12 to 23 Mo.
Sex				
Boys	63	34	19	10
Girls	32	15	10	7
Probable Source of Infection				
Home environment	51	19	17	15
Hospital nursery for the newborn	7	7	..	..
Ward at St. Christopher's	33	21	10	2
Elsewhere	4	2	2	..
Parenteral Infections				
None prior to diarrhea	60	35	13	12
Prior to or concurrent with diarrhea (questionably related)	14	2	7	5
Prior to diarrhea, unrelated	21	12	9	..
Duration Before Admission				
None—onset in hospital	24	17	5	2
None—onset soon after discharge from hospital	8	4	4	..
1 to 2 days	22	9	8	5
3 to 7 days	30	14	7	9
Over 1 week	11	5	5	1
Results				
Died before 48 hours	1	..	1	..
Died after 48 hours	16	13	1	2
Recovered				
1 to 7 days in the hospital	8	1	2	5
8 to 14 days in the hospital	13	5	3	5
15 to 28 days in the hospital	36	16	17	3
More than 28 days in the hospital	21	14	5	2
Totals	95	49	29	17

born (January 15 to 27) reported by Ritter and his associates [6] from the Philadelphia General Hospital; no definite contacts were known to exist. During the remainder of the spring 5 more cases occurred in the hospital. The "diarrhea census" averaged about 4 during May and June.

COMMENT

Inasmuch as the etiologic agent was not known in any of the cases included in this survey (table 1), it is possible that not all of them were

6. Ritter, J. A.; O'Connell, R. R., and Lucente, E.: Infectious Diarrhea of the Newborn, Pennsylvania M. J. **51**:285 (Dec.) 1947.

caused by the same pathogen. Seven of the infants admitted to the hospital because of diarrheal disturbances apparently acquired their disease in nurseries for the newborn in several different hospitals, none of which admitted the existence of an epidemic.

More than 30 per cent of the total number of infants with diarrhea in our hospital contracted the infection while there in spite of the usual isolation precautions; diarrhea developed in as many infants under 3 months of age in the hospital as were admitted with diarrhea. Most of the hospital-contracted infections (table 2) were severe, requiring two to six weeks of hospitalization for the diarrheal disturbance. Careful appraisal of the data on the infants whose diarrhea commenced after admission to the hospital led to the conclusion that most of them became infected in the hospital. Cases of diarrhea which developed in 8 infants soon after their discharge were judged to be hospital infections and were, therefore, included in the group.

Of the 33 infants with hospital-contracted infections, 27 had diarrhea after being in the hospital one to six weeks without abnormal stools. These babies were admitted with a variety of conditions, the majority being respiratory infections (pneumonia, tracheobronchitis, otitis media). Diarrhea was not ascribed to hospital contact when it had been present during the acute primary illness or when it appeared before the infant was afebrile and convalescent. Two infants in the group had been admitted for pylorospasm, 1 for pyloric stenosis, 2 for duodenal adhesions and 1 for atresia of the choanae. One infant 12 months of age had diarrhea on the third day of hospitalization; in 5 infants the onset of diarrhea was only five days after admission and apparently unrelated to parenteral infection. Since the etiologic agent and incubation period were unknown, it was impossible to be certain that these 6 infants had hospital infections, but their conditions were considered as such for the purposes of this study.

The occurrence of 2 fairly well defined epidemics among the infants in the ward also suggested hospital cross infection. During the first epidemic an 8 month old infant (G. L.), convalescent from scurvy, was discharged in apparently good condition. The following day diarrhea developed at home and two days later he was readmitted; four days after this his twin sister had a similar attack, and each of them required about four weeks of hospitalization for diarrhea. In this instance the incubation period appeared to be four to seven days.

The clinical pattern in the majority of instances resembled that usually described for epidemic diarrhea of the newborn. There were profuse yellow, watery stools with little mucus, no pus or blood, no pathogenic organisms on culture and a tendency of the diarrhea to

TABLE 2.—*Cases of Diarrhea of Unknown Origin Developing or Originating in the Ward for Infants of St. Christopher's Hospital for Children during the Period of Study**

Infant	Age	Admitted for	Days in Hospital Before Onset of Diarrhea	Comment	Result	Days After Onset of Diarrhea
P. McA.	16 days	Atresia of choanae	5	No response to sulfonamide drugs, but stools normal after transfusion	Recovered	29
S. C.	2 mo.	Marasmus, prematurity	36	Fair progress until interrupted by onset of diarrhea	Recovered	26
M. P.	15 mo.	Acute nephritis	13	Hematuria and nephrotic syndrome; diarrhea began with epidemic and persisted until death	Died	30
L. H.	5 mo.	Tracheobronchitis	12	Recovered from respiratory infection before onset of diarrhea	Recovered	21
H. E.	2 mo.	Bronchopneumonia	12	Convalescent from pneumonia at onset of diarrhea	Recovered	14
G. L.	8 mo.	Scurvy	†	Epidemic in ward at time of first discharge from hospital	Recovered	35
A. E.	8 mo.	Lobar pneumonia	19	Recovered from pneumonia before onset of diarrhea	Recovered	18
W. D.	5 mo.	Laryngotracheobronchitis	40	Tracheotomy; convalescent before onset of diarrhea	Recovered	21
C. L.	8 mo.	Diarrhea	‡	Infection probably contracted from twin, G. L., who apparently acquired diarrhea in hospital	Recovered	25
G. P.	3 mo.	Otitis media; empyema; osteomyelitis	12	Well on way to recovery when diarrhea started	Recovered	39
J. F.	1 mo.	Pyloric stenosis	§	Diarrhea noted on discharge 14 days after successful operation	Died	58
J. LaR.	1 mo.	Congenital duodenal bands	21	Some vomiting continued after operation, but condition fair until diarrhea began	Died	6
J. C.	3 mo.	Malnutrition	28	Fair progress first month, prior to onset of diarrhea	Died	33
R. L.	9 mo.	Balanoposthitis	11	Recovering from infection at onset of diarrhea (4 days after circumcision)	Recovered	16
R. M.	3 mo.	Nasopharyngitis	8	Ready for discharge when diarrhea began	Recovered	16
L. H.	2 mo.	Pylorospasm	9	Slow progress prior to diarrhea	Died	24
K. A.	3 mo.	Unexplained fever	‖	No sign of enteric infection during first admission; condition undiagnosed	Recovered	28
D. F.	3 mo.	Meningococcic meningitis	22	Convalescent when diarrhea began	Recovered	38
E. C.	2 mo.	Bronchopneumonia; marasmus	18	Responded slowly but recovering prior to onset of diarrhea	Recovered	20
S. P.	3 mo.	Bronchiolitis	13	Recovered from respiratory infection before diarrhea began	Died	28
W. P.	5 mo.	Bronchopneumonia; otitis media	5	Pneumonia cleared promptly and otitis much improved before diarrhea began	Recovered	24
P. K.	4 mo.	Bronchitis	†	Loose stools for 5 days during first admission, but normal stools last 4 days; acute diarrhea and vomiting 24 hours after discharge	Recovered	23
K. B.	5 mo.	Bronchopneumonia	†	Recovered from pneumonia; apparently exposed to ward epidemic	Recovered	21
J. T.	2 mo.	Bronchopneumonia	¶	Recovered from pneumonia; apparently exposed to ward epidemic	Recovered	14
D. E.	6 wk.	Tracheobronchitis	5	Respiratory infection clearing before diarrhea began	Recovered	20
M. S.	2 wk.	Pneumonia	7	Pneumonia cleared (lungs normal at autopsy); diarrhea intractable	Died	19
R.	2 days	Prematurity	5	Weighed 3 lb. 3 oz. (1,446 Gm.) on admission	Died	6
J. S.	2 mo.	Bronchopneumonia	§	Recovered from pneumonia; apparently exposed to diarrhea in ward	Recovered	28
C. K.	3 mo.	Pylorospasm	8	Improving before onset of diarrhea	Recovered	25
M. T.	3 mo.	Tracheobronchitis	5	Respiratory infection clearing before diarrhea began; mongolism	Recovered	14
A. D.	8 mo.	Bronchopneumonia	†	Recovered from pneumonia; apparently exposed to diarrhea in ward	Recovered	26
P. K.	3 wk.	Congenital duodenal bands	10	Diarrhea began 8 days after operation; some vomiting persisted	Died	12
J. V.	12 mo.	Fracture of skull	3	Respiratory infection; stormy course with convulsions	Died	14

* Infants in this table are listed in chronologic order as to date of onset of diarrhea.

† Onset at home, 1 day after discharge.

‡ Onset at home, 4 to 7 days after exposure to twin brother, G. L.

§ Onset at home, day of discharge.

‖ Onset at home, 5 days after discharge.

¶ Onset at home, 3 days after discharge.

persist even in the absence of oral intake. Dehydration developed rapidly, usually without fever or leukocytosis.

Twenty-one of the total of 33 cases of diarrhea contracted in the hospital were in infants under 4 months of age. It is of particular interest, however, that older infants were also involved in the spread in the hospital, although the only deaths among them were in an infant 15 months of age who also had acute nephritis and in an infant 12 months of age who died of the severe injury to the head for which he had been admitted. The other 10 cases arising in the hospital were in infants in the group 4 to 11 months of age. It appears that this type of diarrhea can be acquired and transmitted by older infants but that it tends to be severe only in small or weak ones. Most of those who did recover required long periods of hospitalization.

Of the total of 17 deaths in this series, only 1 occurred within forty-eight hours of admission. Most of the other deaths occurred after a protracted course. Thirteen of the 17 deaths were in infants less than 4 months of age. Eight of these 13 deaths were in infants who acquired the diarrhea in the hospital after being admitted for some other disease.

Therapy, which will not be discussed in detail, was similar to that currently employed in most children's hospitals,[7] consisting of a period of starvation with intravenously and subcutaneously administered fluids, followed by gradually increasing oral intake. Chemotherapy with sulfadiazine was tried in many instances; the consistent lack of success suggested a possible virus origin.

The mode of spread of the diarrheal infection in the ward for infants has not been demonstrated. The most likely manner appears to be through transmission by personnel, although airborne infection has not been excluded. It is believed that persons with infections of the upper respiratory tract entered the ward at times, but there was no apparent relationship of such incidents to the development of diarrheal disease; the infants with diarrhea had no respiratory symptoms. Contamination of formulas was not considered to be an important factor because repeated cultures of formulas did not reveal pathogenic organisms or heavy contamination with saprophytes. Furthermore, many infants who received formulas made in the same milk room did not have diarrhea, and the cases appearing in the hospital did not develop as simultaneously as would be expected if they were caused by contamination of formulas.

Apparently, most of the cases arising in the hospital had their origin from infants with diarrhea who were admitted to the regular ward. There was little cross infection after infants with diarrhea were kept in

7. Glynn, M. J.: Treatment of Epidemic Diarrhea of the Newborn, J. Pediat. 29:205 (Aug.) 1946. Dodd.[8]

a separate ward as described previously. Infants were admitted to that ward, however, with some misgivings, since an infant with diarrhea resulting from one etiologic agent might be exposed to a different intestinal pathogen. The best solution to the problem of cross infection appears to be the provision of facilities for complete individual isolation of all infants admitted to a hospital ward for infants.

SUMMARY AND CONCLUSIONS

Epidemic spread of a disease resembling so-called epidemic diarrhea of the newborn occurred in the wards of a children's hospital on two different occasions. While the mode of spread was not proved, it was thought that breaks in isolation technics by personnel were probably responsible. It appeared that 27, and possibly 33, infants acquired diarrhea in the hospital during a period of eighteen months; 10 of these infants died in spite of the usual forms of therapy.

These observations led to the following conclusions:

1. The spread of diarrheal disease of unknown origin may be a hazard in a ward for infants.

2. As long as the origin and specific treatment of this condition remain unkown, efforts should be made to prevent hospital infections by maintaining each infant quartered in a ward for infants under separate isolation technic.

3. When infants with diarrhea are admitted or when infants acquire diarrhea in the hospital, they should be isolated individually in a section of the hospital as remote as possible from the ward for infants.

7500 Brookfield Road (26).

HEREDITARY FACTORS IN INFANTILE PROGRESSIVE MUSCULAR ATROPHY

Study of One Hundred and Twelve Cases in Seventy Families

SVEN BRANDT
COPENHAGEN, DENMARK

AN OBVIOUS feature of infantile progressive muscular atrophy, as first described by Werdnig [1] and by Hoffmann [2] about fifty years ago, is its familial appearance. This implies that a hereditary factor may play an important part as a cause of the disease. Nevertheless, few attempts have been made to prove this theory and to solve the various genetic problems involved.

Using the sibling method of Weinberg to estimate eventual agreement with mendelian laws, Schimkus [3] in 1934 made a calculation on a number of cases collected from earlier publications and concluded from his results that simple recessive inheritance was probable. Schimkus demonstrated that about 25 per cent of all siblings of the primary patients were paralyzed, which was just what he expected to find in case of recessiveness. He did not realize, however, that such ideal figures can be expected only in unselected material. If Schimkus, as I suppose, really used the proband method, however wrongly named the sibling method, his results are much higher than the ideal figures, which should be between 15 and 18 per cent (Macklin and Mann [4]). This result is much more reasonable, because, as will be explained later in this article, material such as his must always be selected to a certain degree, which means that an excess of abnormal subjects is present.

In one family Hoffmann [2] reported similar disorders among siblings of the mother of the proband. This observation is less consistent with a theory of simple recessive inheritance, as is Benda and Brandt's obser-

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Details of the present study will be published later in a monograph, "Werdnig-Hoffmann Progressive Infantile Muscular Atrophy."

1. Werdnig, G.: Arch. f. Psychiat. **22**:437, 1891; **26**:706, 1894.

2. Hoffmann, J.: Deutsche Ztschr. f. Nervenh. **3**:427, 1893; **10**:292, 1897; **18**:217, 1900.

3. Schimkus, I.: Dissert., Königsberg, 1934.

4. Macklin, M. T., and Mann, H. B.: Fallacies Inherent in the Proband Method of Analysis of Human Pedigrees for Inheritance of Recessive Traits: Two Methods of Correction of Formula, Am. J. Dis. Child. **74**:456 (Oct.) 1947.

vation [5] suggestive of sex-linked recessive inheritance of a condition considered to be infantile progressive muscular atrophy. However, no similar cases have been reported to confirm this last hypothesis.

In 1945, Hanhart,[6] of Switzerland, published 29 cases from 14 families. A high rate of consanguinity was revealed (i. e., in 6 of the 14 families), and this observation was considered by Hanhart as an important argument for assuming recessive inheritance. It appears to me, however, that this result is difficult to evaluate without information concerning the normal rate of consanguinity in a similar population. In fact, frequent inbreeding must be expected in families settled in isolated mountain valleys.

Studies on twins have contributed little to the solution of the genetic problems in this disease. Concordance was reported in four identical pairs of twins (Thomas,[7] Forbus and Wolf,[8] Ford [9] and Thums [10]) and in one nonidentical pair (Pearce [11]). In 6 pairs of twins information concerning identity was lacking or insufficient. Discordance was found in 3 of these 6 pairs.

MATERIAL

In a previous paper the symptoms and course of the disease were described in 112 patients with infantile progressive muscular atrophy, born in Denmark during the last forty years.[12]

The diagnosis for these patients was based on the occurrence of increasing muscular weakness and atrophy, without symptoms of more widespread damage to the upper part of the central nervous system, but resulting in death from involvement of respiratory muscles in early infancy or childhood and in a few children at puberty. The series included 37 patients in whom the original diagnosis was amyotonia congenita (Oppenheim); sufficient supplementary data concerning the symptoms and course of the disease were obtained on follow-up study to justify a reclassification of these last patients, as well as of a few more patients for whom other diagnoses had been made.

Anatomically, 51 of the 112 patients could be classified as having spinal muscular atrophy and 2 or 3 as having the myopathic type, whereas the type of atrophy was not established for 59 patients. The anatomic diagnosis was based on muscle biopsy, electromyographic studies and symptoms such as muscle fibrillation and electric degeneration which, if present, indicated an atrophy of spinal type. In several patients the diagnosis was verified on autopsy. Cases

5. Benda, C. E., and Brandt, G.: Med. Welt **7**:957, 1933.

6. Hanhart, E.: Helvet. pædiat. acta **1**:110, 1945.

7. Thomas, A.: Presse méd. **49**:913, 1941.

8. Forbus, W. D., and Wolf, F. S.: Bull. Johns Hopkins Hosp. **47**:309, 1930.

9. Ford, F. R.: Diseases of the Nervous System in Infancy, Childhood and Adolescence, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1944.

10. Thums, K.: Ztschr. f. d. ges. Neurol. u. Psychiat. **162**:233, 1938.

11. Pearce, N. O.: Amyotonia Congenita, Am. J. Dis. Child. **20**:393 (Nov.) 1920.

12. Brandt, S.: Course and Symptoms in Progressive Infantile Muscular Atrophy, Arch. Neurol & Psychiat., to be published.

observed in siblings of patients in whom a type diagnosis had been made were considered of the same type even when no other information was available than such as indicated a clinical picture of similar nature. Cases in which the original diagnosis of infantile progressive muscular atrophy seemed uncertain or had to be changed as a result of the follow-up study were, of course, omitted from the material.

RESULTS OF GENETIC STUDIES

Frequency of the Disease.—This can be calculated with only coarse approximation. The 112 cases were observed through the last forty years in a population of between 4,000,000 and 5,000,000. I feel, however, that many cases have not been recognized. From 1943 to 1947, all new cases in Denmark—about 20—have come to my attention, that is, 5 new cases every year, or 1 patient in 1,000,000 inhabitants.

Sexual, Geographic and Seasonal Distribution.—Fifty-seven of the 112 patients were boys and 55 girls. No variations could be found in geographic distribution within Denmark. In a smaller group of 52 children in whom the onset of weakness could be approximately established, the disease occurred with about the same frequency in all months of the year.

Stillbirths and Abortions Among Siblings of the Probands.—In the 70 families studies, 27 of 247 pregnancies resulted in miscarriage, which means 1 miscarriage in 9.3 pregnancies. In a control group with 876 pregnancies, 90 miscarriages were recorded, i. e., one of 9.7 pregnancies. These figures indicate that no significant excess of miscarriages is present in my material.

No symptoms suggestive of progressive muscular weakness were observed in any of the parents of the patients.

Only 7 per cent of the patients survived the age of 15 years. Progeny of patients with infantile progressive muscular atrophy have never been reported in the literature, nor were any observed in this study.

Determination of the Type of Inheritance by Weinberg's Methods.—The study included 70 families among which two mothers were married twice; from both marriages children with paralyses were born. In 18 of the families the proband was the only child. Data on the remaining 52 families from which calculations could be made are presented in the table. In this table the firstborn child with the disease in each family is placed in the fourth column. All older siblings are found in the third and all younger siblings, both normal children and patients, in the fifth column.

Excluded from the following calculations are (1) stillbirths and abortions, which are labeled (*s*) in the table and (2) all children younger than 1 year of age in whom no symptoms of paralysis had been observed. Some of them died from irrelevant causes; some were

Families with One or More Children with Infantile Progressive Muscular Atrophy *

Family No.	Case No.	Older Siblings	Proband	Younger Siblings
I	1, 2	.....	p†	p n
	4	n	p	.....
II	5, 6	n n n	p	n n n p
III	7 to 9	.....	p	(s) n n p p
IV	10, 11	n	p	p (s)
V	13 to 15	n n	p	p p
VI	16 to 18	.....	p	n n n p p
VII	19 to 21	.....	p	n n n p p
	22	n n	p	.....
VIII	23, 24	.....	p	p n n n
	26	n	p	.....
IX	27, 28	.....	p	p
X	29, 30	(n)	p	n n p
XI	32 to 34	n n	p	p n (s) (n) (n) p
XII	35, 36	.....	p	p n
	37	n n	p	(s) (s) n n
XIII	38	n	p	n
XIV	39, 40	.....	p	p (s) n
XV	41, 42	.....	p	p n
XVI	43 to 48	.....	p	p p p p n n n n p n
XVII	51, 52	.....	p	(n) (n) p
	53	.....	p	n n
XVIII	55, 56	n	p	p
	58	n n	p	.....
	61	n	p	(n)
XIX	62	n	p	.....
XX	64, 65	.....	p	p
	66	n	p	n n n
	67	n	p	n (s) (s) n n
XXI	68, 69	n n n	p	p
XXII	70, 71	n	p	p
	72	.....	p	(n)
XXIII	73 to 75	.....	p	(s) p p
	76	n	p	.....
	77	n n	p	.....
	78	(s) (s) (s)	p	n
XXIV	79, 80	n n n	p	n n p n
	81	n (n)	p	.....
XXV	82, 83	(s) (s)	p	(s) p
XXVI	85	n (s) (s) (n)	p	.....
XXVII	87 to 89	.....	p	p p
XXVIII	90, 91	n	p	n p
XXIX	.....	.....	p‡	.....
	92	.....	p	(s) n n
	93	.....	p	(s) n
	96	.....	p	n
	98	n	p	n
XXX	99	n n	p	(n)
XXXI	101, 102	n (s)	p	p
XXXII	103 to 105	(s) n	p	(s) (n) p n p
XXXIII	106, 107	n	p	p n n n (n)
XXXIV[a]	108, 109	.....	p	p n n n
XXXIV[b]	110, 111	.....	p	n n p (s) (s) (s) (s)

* The family and case numbers used in this table correspond to those used in the author's coming monograph.

† Paralyzed children are indicated by p, normal children by n, children without symptoms of paralyses who died before 1 year of age or who were alive but less than 1 year old at the time of study by (n) and stillbirths and abortions by (s).

‡ Only child.

alive at the time of the study. Children belonging to the last group are labeled (*n*) in the table.

If Weinberg's proband method (correctly used as recently emphasized by Macklin and Mann) is applied to the remaining children, the disease is found present in 42 (or 30 per cent) of the 139 siblings of the 52 probands.

If Weinberg's sibling method is used, in which every patient in each family is considered a proband once and every family is counted as many times as it contains patients, the disorder is found in 120 (or 38 per cent) of 313 siblings of the 94 probands.

Consanguinity Rate.—Consanguinity was reported in 3 of 68 families. However, in 1 family consanguinity occurred in two generations, both with paralyzed children. For this reason, I calculated four consanguinities among 69 families, counting this last family twice. The result of this calculation is a consanguinity rate of 5.8 per cent.

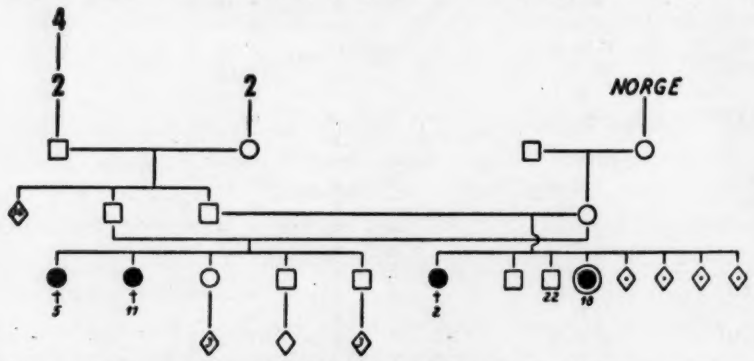

Fig. 1.—Pedigree of family XXXIV showing paralyzed children resulting from the successive marriages of a woman to 2 brothers. Symbols used are as follows: signifies a normal male offspring 5 years of age whose parents and 4 grandparents were registered in my genetic file; numbers under the symbols represent age in years, and death is indicated by a cross. indicates a normal female with Norwegian ancestors. ◈ symbolized 3 siblings of unknown sex. ▣ indicates the proband. ⊡, ⊙ and ◈ signify miscarriages. The solid circles and squares indicate other paralyzed children.

This result was obtained by asking the parents simply whether they were aware of any common ancestors. It should be emphasized, however, that a genetic file, containing complete information regarding personal data on antecedents in 30 families as far back as the great-great-grandparents and in 40 families as far back as the great-grandparents, revealed no consanguinity not known before by the parents of the probands.

Variability.—In one family with 2 patients, a third child probably had an abortive type of the disease. The girl, 6½ years old, had some difficulty with running. Neurologic examination showed absence of both knee reflexes and slightly diminished power in the muscles of the buttocks. Except for this single observation, no definite intrafamilial variability in cases among siblings could be noted in the material. On the other hand, some interfamilial variation was probably present,

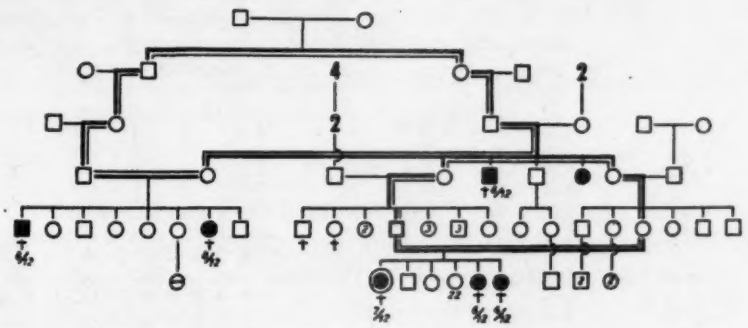

Fig. 2.—Pedigree of family VI in which consanguinity was recorded in two generations. See legend to figure 1 for explanation of symbols. ⊖ indicates offspring with mental deficiency.

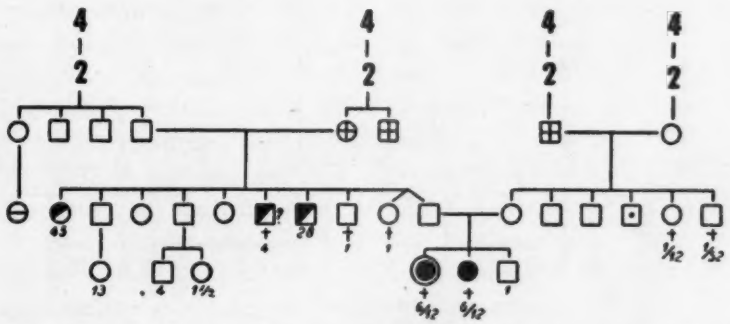

Fig. 3.—Pedigree of family I. See legend to figure 1 for explanation of symbols. ⊕ indicates persons with insanity and ◩ persons with symptoms of myopathy.

because the disease in some families had a much more rapid course in all sick members than was noted in other families.

Twins.—Two pairs of nonidentical twins are included in the material. In both pairs only one child was paralyzed; the other was normal.

Observations Made on Single Pedigrees.—Although the disease in most families included in this study was limited to one generation, a few exceptions were reported.

Family XXXIV (fig. 1).—In this family the same woman was married successively to two brothers. Among the offspring of both marriages paralyzed children were found.

Family VI (fig. 2).—As mentioned previously, consanguinity was recorded in two generations in this family, first reported on in 1920 by Krabbe.[13] My studies resulted in the addition of 2 more patients. In a third branch of this family the disease appeared among the offspring of parents who were not related.

Family XXX.—The mother of the proband in this family had another child, also paralyzed, by a man not related to the father of the proband.

Family I (fig. 3).—In this family 3 siblings of the father had muscular disorders. Two of them were examined by me. A severe muscular atrophy was observed. The type of atrophy could not be established, but the age of

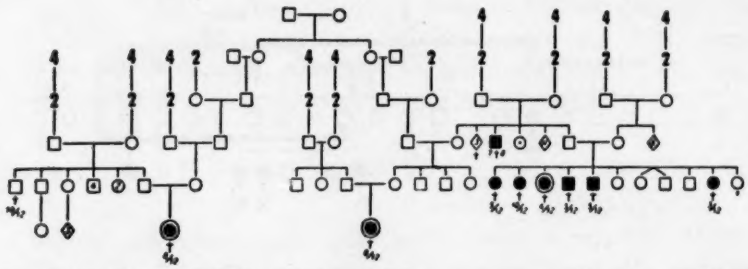

Fig. 4.—Pedigree of family XVI showing common antecedents for 3 probands, one of which had several paralyzed siblings. See legend to figure 1 for explanation of symbols.

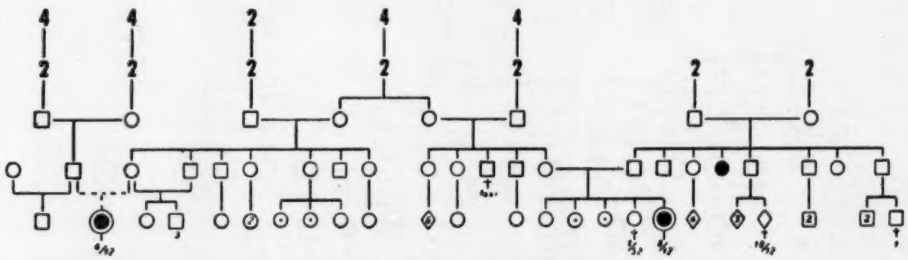

Fig. 5.—Pedigree of family XXIV showing common antecedents for two other probands. See legend to figure 1 for explanation of symbols. Dotted lines indicate that the child's mother and father were unmarried.

these 2 patients, 28 and 45 years, made it probable that a myopathy was present. In fact, this was the original diagnosis made on examination of one of them in a university clinic. The spinal nature of the disease in the proband was verified on autopsy.

Family XVI (fig. 4).—Common ancestors were discovered for 3 probands in the study who were not siblings. One had several paralyzed siblings and an uncle

13. Krabbe, K. H.: Congenital Familial Muscular Atrophies and Their Relation to Amyotonia Congenita, Brain **43**:166, 1920.

with a history of crippling and inability to talk who died at the age of 8 years. It is possible that his disorder was of a different kind.

Family XXIV (fig. 5.)—Common ancestors were discovered for 2 other probands in my material whose mothers were related. In the family of the father of one of these patients a sister died at the age of 8 months from a progressive weakness similar to the disease in the proband.

Family XIX.—An uncle was treated at an orthopedic clinic for progressive muscular weakness. A history of congenital paralysis was noted in two of the father's cousins. They died at the ages of 16 months and 16 years.

Family XXIX.—The family history indicated a disabling muscular weakness in the proband's paternal great aunt, followed by death at the age of 10 years.

Family XIII.—Four paternal second cousins of the proband died of muscular weakness between the ages of 2 months and 14 years.

COMMENT

Before any conclusions are made from the presented observations, nonhereditary factors which might cause familial illness should be eliminated. The mothers of practically all the patients were questioned by me about (*a*) their living conditions during pregnancy, especially regarding food and its vitamin content, (*b*) diseases during pregnancy, (*c*) symptoms in the newborn baby indicating injury at birth or intrauterine infection and (*d*) symptoms of infectious disorders observed during the infant's first months of life. Even though a certain number of positive answers were obtained, none were consistent enough to warrant positive conclusions regarding their etiologic value. Forty-three children had negative blood Wassermann reactions. In 4 cases the blood of both the mother and child was found to be Rh positive. In 27 children examined normal eyegrounds were observed.

The observations on the few pairs of twins with infantile progressive muscular atrophy which can be collected from the literature and from my studies are consistent with the hypothesis of inheritance as the main cause of the disease: Discordance was observed in none and concordance in 4 pairs of identical twins, whereas discordance was seen in 2 and concordance in 1 of 3 pairs of nonidentical twins. Further studies on twins are, however, needed before reliable conclusions can be made.

So far the familial occurrence is best explained on the basis of an inherited factor. The following circumstances should be considered regarding the type of inheritance.

The fact that the sexes are equally represented rules out the possibility of sex-linked recessive inheritance. For this reason the observation of Benda and Brandt mentioned previously must be considered as an exception.

Because all the parents of children with infantile progressive muscular atrophy in this study were without any symptom indicating similar

disorders, the possibility of simple conduction of a dominant factor can also be ruled out. In case of dominance, therefore, the dominant factor must have been introduced in one of the parents by mutation. As the patients never have children of their own, no opportunity is available to observe whether such a hypothetic mutated factor will manifest itself in the next generation and in this way prove its dominant nature.

The figures obtained from the calculations with Weinberg's methods are much higher than the ideal figures which may be expected from unselected material in case of simple recessiveness, these being 15 to 18 per cent when the proband method is used and 25 per cent when the sibling method is used. On the other hand, the result is lower than should be expected in simple dominance, the ideal figures for dominance being 30 to 40 per cent with the proband method and about 50 per cent with the sibling method. Finally, it should be stated that the figures obtained may always be consistent with atypical dominance in which the manifestation of the dominant factor for some reason is incomplete.

One may take the view that some of the genetically abnormal infants die in utero, and, therefore, fewer abnormal children are born than should be expected in case of simple dominance, which type of inheritance actually may be present in spite of the figures obtained by Weinberg's methods. As mentioned previously, however, no reliable excess of miscarriages could be observed in my material. I feel, therefore, that this view cannot be substantiated.

The question remains, consequently, whether the results of this study should lead to the conclusion either that the inheritance was dominant with incomplete manifestation or that a recessive factor was present, the high figures obtained by Weinberg's methods being a result of an excess of paralyzed patients in the material because of selectivity. There is, in fact, much evidence that this material is selected, which means that a certain number of families with only 1 sick child and perhaps several healthy children are not included.[14] The reason for this is that many primary patients are recognized only when a second child in the same family has similar symptoms and is brought to a hospital in time to be studied. In case no younger siblings show paralysis the first child will perhaps never come to any physician's attention, nor will any of the healthy siblings born in that family.

The frequency of consanguineous marriages recorded in my material (5.8 per cent) was compared with the rate in a control series including

14. It should be kept in mind that the kind of selectivity which is caused from inaccessibility of those families in which only healthy, heterozygous children, but no homozygous paralyzed children, were born was corrected for by using the Weinberg method; this kind of selectivity should not be confused with the aforementioned type.

290 families. In this control series two consanguineous marriages were reported (0.7 per cent). This percentage of inbreeding in families with the disorder is indeed considerably lower than Hanhart's finding (40 per cent), mentioned previously. However, as stated, Hanhart's result is of a rather limited value, since no comparison was made with the average frequency of consanguineous marriages in the population examined. Even though my observations have not completely confirmed Hanhart's results, an excess of consanguineous marriages was found in my series, these being about eight times more frequent than in my controls. The hypothesis of recessive inheritance is supported by this observation.

On the other hand, symptoms of progressive paralyses are reported among relatives other than siblings in so many families (9 of 68) that some skepticism may be justified regarding recessive inheritance as a general rule in this disorder. It should be mentioned that no clinical or anatomic difference could be seen between the cases observed in the probands belonging to these 9 families and those in probands belonging to other families. The small number of myopathic cases in my series (less than 6 per cent) is not restricted to these 9 families. Unfortunately, these more distantly related instances could not be studied further except in one family (family I) in which the sick relatives were still alive. The existence of the remaining cases and the symptoms recorded are based only on information obtained from relatives. Therefore, these cases have not been included in the 112 constituting the diagnostically unquestionable material. Nevertheless, I feel that the information gleaned concerning these relatives cannot be completely disregarded. Even though observations in two families (families VI and XXXIV) are fairly consistent with the hypothesis of recessive inheritance, this is hardly the case in the remaining 7 families, unless it is assumed that heterozygous persons have been exceptionally frequent in the communities of these families. The geographic distribution of the patients, as well as that of their antecedents gives no support to this assumption.

I feel, therefore, that dominance with incomplete manifestation must be taken into consideration in some families. Observations by Hoffmann,[2] Steindler,[15] Chatterjee [16] and Hurwitz and Gerstle [17] support this point of view.

That not only one pair of genes but probably many co-acting pairs may be responsible for the disease seems indicated by the interfamilial

15. Steindler, R.: Arch. f. Kinderh. **106**:235, 1935.

16. Chatterjee, S. C.: Indian J. Pediat. **4**:190, 1937.

17. Hurwitz, S., and Gerstle, M.: Amyotonia Congenita with Familial Incidence, Arch. Neurol. & Psychiat. **33**:1317 (June) 1935. "Amyotonia congenita" is the diagnosis used in the two last-mentioned publications. However, the patients reported on have typical progressive muscular atrophies from my point of view.

variability found. The single abortive case which I observed seems to necessitate more complicated explanations. Finally, even though intrafamilial variability is rare in siblings, such variability is more pronounced in a few families in which more distant relatives were paralyzed (see data on family I). These observations suggest the existence of co-acting pairs of genes, modifying the severity and progression rate of the disease.

SUMMARY AND CONCLUSION

The following conclusions are made from genetic studies including 70 families with 112 cases of infantile progressive muscular atrophy among siblings and a few further similar cases among more distant members of the families:

Recessive inheritance, causing the disease to appear in homozygous persons born of two conductors, is the likely cause in most cases. A consanguinity rate of 5.8 per cent, which is eight times higher than that observed in a control group, as well as calculations by means of Weinberg's methods, justifies this conclusion, when the selectivity of the material is taken in consideration.

However, a few observations are less consistent with recessive characteristics and seem to necessitate the more flexible hypothesis of incomplete dominance for some families.

Interfamilial variability regarding course and severity was frequent, whereas intrafamilial variability among siblings was observed only once, an abortive case present in one family. In the few families in which more distant family members had the disorder, variability was more frequent. These observations suggest that more complicated genetic factors may be present, such as two or more co-acting genes, modifying the severity and the rate of progression of the disease.

Rymarksvej 58, Hellerup.

PERITONEAL IRRIGATION

Method of Treatment of Acute Renal Failure in an Infant

WALTER R. BUERGER, M.D.
EDWARD C. LAMBERT, M.D.
AND
BARBARA A. MAITLAND, B.A.
BUFFALO

UNLESS the patient with acute renal failure can rid himself of the waste products usually eliminated by the glomeruli of the kidney, he cannot long survive the resulting chemical imbalance. The chief aim of medical therapy, therefore, is to reestablish glomerular filtration or to remove waste products by some means other than the kidney. Recently, two successful methods of treatment by extrarenal pathways were demonstrated for adults with renal insufficiency. Kolff and Berk [1] submitted the uremic patient's circulating blood to dialysis outside the body. Fine, Frank and Seligman [2] used the peritoneum as a dialyzing membrane by irrigating the peritoneal cavity with fluid and removing the diffusible waste products. A review of 27 cases in which the patients were treated by peritoneal irrigation was presented by Odel and Ferris,[3] and other instances in which this procedure has been used were also described.[4] None of the patients reported on was an infant.

From the Children's Hospital and the Department of Pediatrics, University of Buffalo School of Medicine.

a Great Area, Acta med. Scandinav. **117**:121-134, 1944.

1. Kolff, W. J., and Berk, H. T. J.: The Artificial Kidney: A Dialyzer with

2. Fine, J.; Frank, H. A., and Seligman, A. M.: The Treatment of Acute Renal Failure by Peritoneal Irrigation, Ann. Surg. **124**:857-878 (Nov.) 1946.

3. Odel, H. M., and Ferris, D. O.: The Treatment of Acute Renal Insufficiency with Peritoneal Lavage, Proc. Staff Meet., Mayo Clin. **22**:305-313 (Aug. 6) 1947.

4. Doenges, J. P., and Strahan, C., Jr.: Treatment of Acute Sulfadiazine Anuria by Continuous Peritoneal Lavage: Case Report, Bull. School Med. Univ. Maryland **31**:89-99 (Jan.) 1947. Robertson, H. R., and Rutherford, P. S.: Peritoneal Irrigation in the Treatment of Renal Failure Due to Transfusion Reaction, J. Lab. & Clin. Med. **32**:982-987 (Aug.) 1947. Muirhead, E. E.; Small, A. B.; Haley, A. E., and Hill, J. M.: Peritoneal Irrigation for Acute Renal Damage Following Incompatible Blood Transfusion: A Discussion Based on Three Cases, ibid. **32**:988-1001 (Aug.) 1947. Goodyear, W. E., and Beard, D. E.: The Successful Treatment of Acute Renal Failure

(Footnote continued on next page)

Although the infant patient to be reported on here died eventually, the application of the method proved successful in that it provided an adequate excretory route as a substitute for the kidney for eight and one-half days. Within this period, the blood nonprotein nitrogen level fell from 178 mg. per hundred cubic centimeters to normal, and parallel improvement occurred in the infant's general condition. The cause of the renal failure, however, persisted and eventually led to the patient's death.

REPORT OF A CASE

R. M., a girl 8 months of age, entered the Children's Hospital May 2, 1947, because of pallor and loss of appetite. She had been well until four days before her admission, when she appeared pale, and on the following day she refused part of her feedings and vomited once. There was no history of urinary symptoms. Family history and past history were not remarkable. Developmental history was normal.

Physical examination revealed a pale, irritable, listless baby, weighing 20 pounds (9,072 Gm.). The temperature was 100.6 F. Although the blood pressure was 196 systolic and 46 diastolic, the heart was of normal size. Enlarged kidneys were palpated in both flanks. The infant was not voiding. The reaction of a small amount of urine obtained by catheterization was strongly positive for albumin, and the sample contained 10 white and 30 red blood cells per high power field, as well as many gram-negative and gram-positive bacteria. Culture of the urine revealed colon bacilli and nonhemolytic streptococci. The blood nonprotein nitrogen level was 136 mg. per hundred cubic centimeters. Examination of the blood revealed a hemoglobin level of 5.7 Gm. per hundred cubic centimeters and a white cell count of 24,400, with a predominance of immature neutrophilic leukocytes. Blood and bone marrow pictures were consistent with hypochromic anemia and excessive regenerative response of both red and white elements.

For convenience, we divided the course of the disease into four time periods:

I. *Period of Pronounced Azotemia, First to Fifth Days.*—Streptomycin and penicillin were administered throughout the course in the hospital. As shown in figure 1, during the first six days the urinary output remained less than 50 cc. per day and the urine contained large quantities of thick mucoid material. Obstruction to the urinary pathways was, therefore, considered, and ureteral catheterization [5] was attempted on the third day. This was unsuccessful since the ureteral orifices could not be identified because of the severe edema of the wall of the bladder. A cystogram showed a small, contracted, irregular bladder. Still in hope of relieving a possible ureteropelvic block or renal edema, the left kidney was

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by Peritoneal Irrigation, J. A. M. A. **133**:1208-1210 (April 19) 1947. Grossman, L. A.; Ory, E. M., and Willoughby, D. H.: Anuria Treated by Peritoneal Irrigation, ibid. **135**:273-275 (Oct. 4) 1947. Strean, G. J.; Korenberg, M., and Portnoff, J. C.: Acute Uremia Treated by Peritoneal Irrigation, ibid. **135**:278-279 (Oct. 4) 1947. Bassett, S. H., and others: Nitrogen and Fluid Balance in Treatment of Acute Uremia by Peritoneal Lavage: Analysis of Peritoneal Washings for Protein, Nonprotein Nitrogen and Phosphorus, Arch. Int. Med. **80**:616-636 (Nov.) 1947.

5. All surgical procedures were performed by Dr. Baxter Brown, attending urologist on service.

explored on the fourth day. The kidney was enlarged to adult size, inflamed and tightly encapsulated; no abnormality of the ureter or pelvis was detected. The left renal capsule was stripped, but impending shock prevented repetition of the same procedure on the opposite side. On the fifth day, blood nonprotein nitrogen had risen to 178 mg. per hundred cubic centimeters, and the blood pressure to 240 systolic and 80 diastolic. Death from uremia seemed imminent.

At this stage, it seemed clear that unless uremia could be controlled, life could not be sustained longer than a few days. On the other hand, if the child could be tided over a period of oliguria until the urinary tract infection could be controlled, there was a possibility of recovery. Accordingly, the procedure of peritoneal irrigation was instituted.

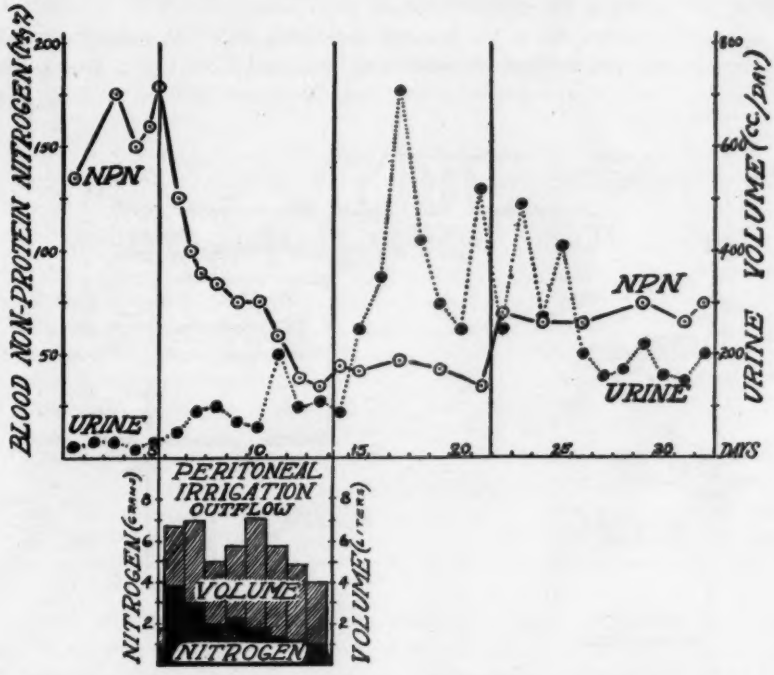

Fig. 1.—Graph showing azotemia as related to urinary output and peritoneal irrigation in an infant with acute renal failure.

II. *Period of Peritoneal Irrigation, Fifth to Fourteenth Days.*—The technic of peritoneal irrigation was essentially that used by Fine and his associates [2] and others on adults (fig. 2). On the fifth day in the hospital, bilateral McBurney incisions were made, and no. 20 rubber mushroom catheters, with additional holes cut in shafts and tips, were inserted into the right and left peritoneal cul-de-sacs. The incisions were closed in layers snugly around the catheters to prevent leakage. Plugging of catheters is a major problem mentioned in most of the cases reviewed. In our case, it was relieved by the addition of an apparatus to allow reversal of flow and a special bottle to permit intermittent suction. Plugging occurred twice in the first twelve hours. Subsequently, the inflow was continuous for eight days at the average rate of 200 to 300 cc. per hour, the outflow corresponding to the inflow.

The irrigation solution used at the start was essentially the modified Tyrode's solution suggested by Fine and his co-workers[2] (table 1). Streptomycin was added instead of sulfadiazine because of the fear of additional renal damage from the latter in the presence of oliguria. In the preparation of the solution, sterile sodium bicarbonate, heparin, penicillin and streptomycin solutions were not added until the other constitutents had been autoclaved.

Because of changing clinical, blood chemical and bacteriologic findings, it was necessary to adjust the composition of the irrigation solution from time to time. The following changes were made (table 1):

1. On the sixth day in the hospital in order to relieve edema, the solution was made hypertonic by increasing the glucose from 1.5 to 20 Gm. per liter. This change also provided additional calories.

2. On the seventh day in the hospital, sodium chloride was reduced from 8 to 6 Gm. per liter and the sodium bicarbonate increased from 1 to 2 Gm. per liter

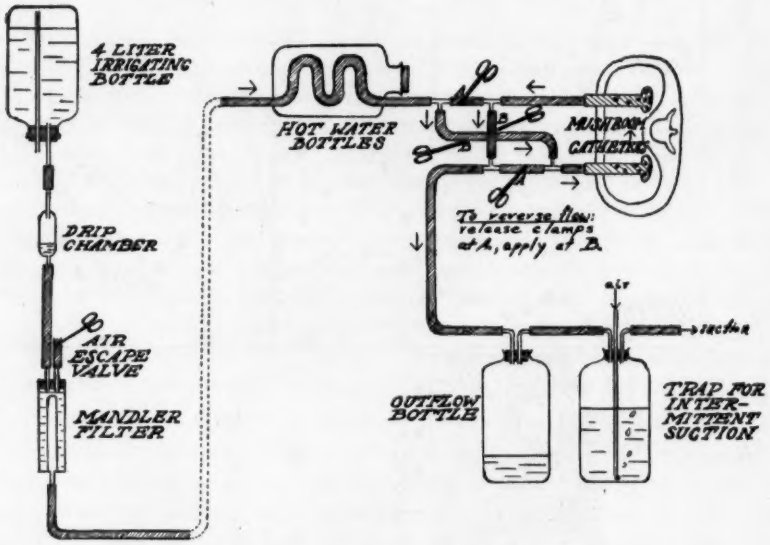

Fig. 2.—Diagram of peritoneal irrigation system.

to relieve edema and to lower blood chlorides. This also resulted in a decrease in the total sodium in the irrigation solution.

3. On the tenth day in the hospital the dose of penicillin and streptomycin was doubled to prevent complications from peritonitis (cultures of the irrigation fluid yielded Staphylococcus aureus, which organism gave a negative reaction to the coagulase test in the inflow and showed Aerobacter aerogenes in the outflow).

Figure 3 and table 2 show the chemical changes of the blood and the effects of the aforelisted adjustments of the peritoneal irrigation fluid with respect to chloride, sodium, potassium, calcium, phosphorus, glucose and nonprotein nitrogen. In spite of negligible intake of sodium chloride by other routes, the previously low blood chloride content rose to slightly high levels when the concentration of chloride in the inflow solution was high. When the chloride in the inflow was reduced to a concentration approximating that normally seen in the blood,

the blood level fell to nearly normal. Unfortunately, the sodium in the inflow solution was reduced to a concentration below that of the blood, and this was reflected by a fall in blood sodium to subnormal values. The persistence of low blood levels of potassium and calcium during the irrigation can be attributed to their low concentration in the inflow. The reason the concentration of phosphorus in the outflowing peritoneal irrigation fluid was higher than that in the inflow or in the blood remains unexplained. The lower concentration of glucose in the outflow, as compared to that in the inflow, was due to absorption of glucose into the blood stream. The rapid fall of blood nonprotein nitrogen during the irrigation period was paralleled by a decrease in the nonprotein nitrogen products in the outflowing peritoneal irrigation fluid. Blood urea clearance by the peritoneal route on the fifth day of irrigation was 2.3 cc. per minute and on the sixth day 3.4 cc.

As shown in figure 1, after forty hours of peritoneal irrigation with approximately 12 liters of fluid, the blood nonprotein nitrogen was reduced from 178 to

TABLE 1.—*Composition of Irrigation Solution*

Solutes per Liter of Distilled Water	Initial Solution, Gm./L.	Adjusted Solution, Gm./L.
Sodium chloride (NaCl)	8.0	6.0
Potassium chloride (KCl)	0.2	0.2
Calcium chloride ($CaCl_2.2H_2O$)	0.1	0.1
Magnesium chloride ($MgCl_2.6H_2O$)	0.1	0.1
Sodium acid phosphate (NaH_2PO_4)	0.05	0.05
Glucose	1.5	20.0
Sodium bicarbonate	1.0 Gm.	2.0 Gm.
Heparin	0.25 mg.	0.25 mg.
Penicillin	2,500 units	5,000 units
Streptomycin	10 mg.	20 mg.

87 mg. per hundred cubic centimeters, although urinary output was still less than 100 cc. per day. Blood pressure, however, had risen to 300 systolic and 210 diastolic. Generalized edema became prominent during the first few days of peritoneal irrigation but gradually subsided after the concentration of glucose in the irrigation fluid was increased and that of chloride decreased. The temperature remained essentially normal until the seventh day, when it rose to 101.6 F. It fluctuated between normal and 103 F. throughout the remainder of the period of irrigation. Blood cultures remained sterile. Infection of the urinary tract was still evidenced by small samples of urine loaded with white blood cells and cultures positive for Escherichia coli which were found to be resistant to streptomycin. In spite of risk of additional damage to the kidney, administration of sulfadiazine was begun in divided doses, with a daily total of 0.4 Gm., on the thirteenth day in the hospital. On that day, because of the normal blood nonprotein nitrogen values for two days, peritoneal irrigation was permitted to slow down. It was discontinued on the fourteenth day in the hospital after eight and one-half days of irrigation, at which time the blood nonprotein nitrogen level was 44 mg. per hundred cubic centimeters. The mushroom catheters, however, were left in place for possible future use.

III. *Period of Slight Azotemia, Fourteenth to Twenty-First Days.*—Sulfadiazine was continued after peritoneal irrigation was stopped, but on the seventeenth day in the hospital it was changed to a combination of sulfathiazole, 0.15 Gm., and sulfadiazine, 0.15 Gm., daily. On that day only 30 white blood cells per high power field were present in the urine; the blood pressure was 176 systolic and 110 diastolic, and urinary output had increased to 712 cc. Because of the increased urinary output the mushroom catheters were removed at this time.

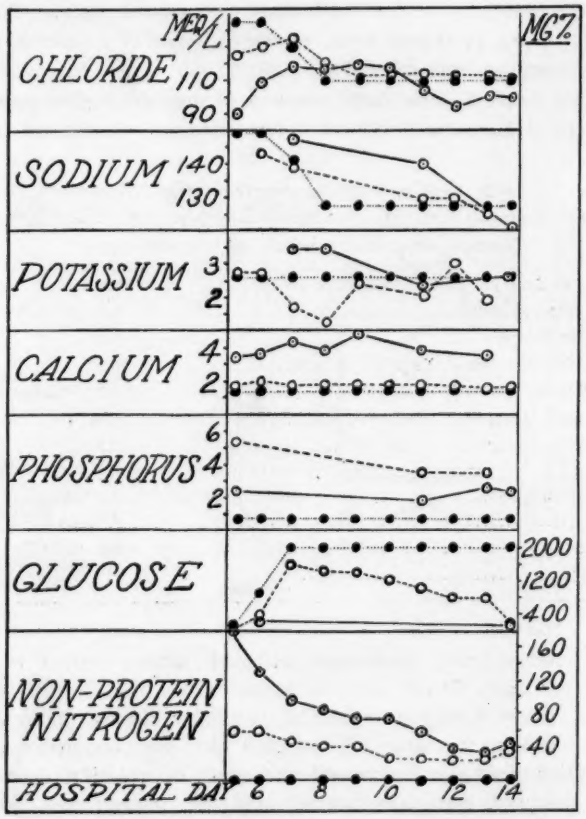

Fig. 3.—Graphs showing constituents of blood and irrigation fluid. Circles with dots represent values for blood, solid circles, values for inflowing irrigation fluid and open circles, values for outflowing irrigation fluid.

Subsequently, the patient continued to void 250 to 500 cc. per day. Sulfathiazole and sulfadiazine were gradually increased to 0.375 Gm. of each daily. Blood nonprotein nitrogen again fell to 36 mg. per hundred cubic centimeters. Urine contained only 10 white and 10 red blood cells per high power field, but specific gravity was fixed between 1.006 and 1.010. The temperature remained essentially normal from the fifteenth to the nineteenth days in the hospital, when it rose to 101.6 F. On the twenty-first day in the hospital, seven days after discontinuation of peritoneal irrigation, the prognosis appeared hopeful.

IV. *Period of Moderate Azotemia, Twenty-Second to Thirty-Second Days.*—The patient's subsequent hospital course was downhill. On the twenty-second day in the hospital, she had generalized convulsions. At that time blood calcium was 3.8 milliequivalents per liter (7.5 mg. per hundred cubic centimeters). Five grams of calcium gluconate U. S. P. was given intravenously, and 3 to 4 Gm. of calcium lactate U. S. P. was given orally for three days. The temperature rose to 104.8 F. On the same day the urine was loaded with red blood cells and clots, and blood nonprotein nitrogen rose to 70 mg. per hundred cubic centimeters. While the blood in the urine might conceivably have been due to

TABLE 2.—*Values for Various Constituents of Blood and of Inflowing and Outflowing Peritoneal Fluid During Period of Irrigation*

	Day in the Hospital									
	5	6	7	8	9	10	11	12	13	14
hloride (mEq./L.)										
Inflow	142	142	132	108	108	108	108	108	108	108
Outflow	125	131	138	121	110	113	116	113	113	111
Blood	88	107	119	117	122	117	105	95	102	100
dium (mEq./L.)										
Inflow	149	149	142	127	127	127	127	127	127	127
Outflow	...	143	138	...	...	...	129	130	124	...
Blood	...	...	149	...	...	...	140	...	...	119
tassium (mEq./L.)										
Inflow	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7	2.7
Outflow	2.8	2.8	1.7	1.4	2.5	...	2.1	3.0	1.8	...
Blood	...	...	3.4	3.4	...	...	2.3	...	...	2.7
lcium (mEq./L.)										
Inflow	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4	1.4
Outflow	1.7	2.0	1.7	1.8	1.8	1.8	1.9	1.7	1.6	1.6
Blood	3.4	3.6	4.3	3.9	4.8	...	3.9	...	3.5	...
osphorus (mEq./L.)										
Inflow	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8
Outflow	5.4	...	...	...	...	...	3.7	...	3.5	...
Blood	2.4	...	...	...	...	...	1.9	...	2.6	2.4
cose (mg./100 cc.)										
Inflow	150	900	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Outflow	2	370	1,380	1,320	1,280	1,210	1,060	800	800	190
Blood	...	221	....	....	....	....	....	...	...	176
nprotein nitrogen (mg./100 cc.)										
Outflow	60	59	45	39	38	25	24	26	26	37
Blood	178	130	94	83	76	75	58	38	34	44
ea nitrogen (mg./100 cc.)										
Outflow	48	43	28	21	24	26	26	26	26	26
Blood	..	..	..	..	42	36	..	..	..	..
tal volume (cc.)										
Inflow	1,400	6,700	6,900	4,800	5,250	7,050	5,900	5,075	4,075	650
Outflow	1,560	6,440	6,640	5,190	5,800	6,840	5,880	4,680	4,180	310

erosion of the mucosa of the urinary tract, it was also possible that the sulfonamide compounds were the cause, so they were discontinued at once. At that time, the free sulfonamide level in the urine was only 3.4 mg., the total sulfonamide content only 55 mg. and the free sulfonamide level in the blood 4 to 6 mg., per hundred cubic centimeters.

The subsequent course in the hospital indicated that it might have been advisable to continue sulfonamide therapy in spite of hematuria. On the twenty-fifth day in the hospital, the urine contained no red blood cells but was loaded with white blood cells; this condition persisted throughout the remainder of hospitalization. The specific gravity of the urine continued between 1.008 and 1.013 and urinary output, between 150 and 225 cc. per day. Blood nonprotein nitrogen rose to 75 mg. per hundred cubic centimeters (fig. 1). Renal

urea clearance was only 12 per cent of normal. Methenamine U. S. P., 0.6 to 1 Gm. daily, was unsuccessful in controlling the infection of the urinary tract. The patient became steadily more and more edematous, although the blood sodium chloride levels were normal and total protein remained above 5 Gm. per hundred cubic centimeters of blood. Blood calcium was 11.6 mg. on the twenty-sixth day in the hospital; calcium chloride, 1 Gm. by mouth, was begun in order to maintain an acid urine in which methenamine might be effective. Subsequently, 4 Gm. of calcium chloride was administered daily by mouth until the

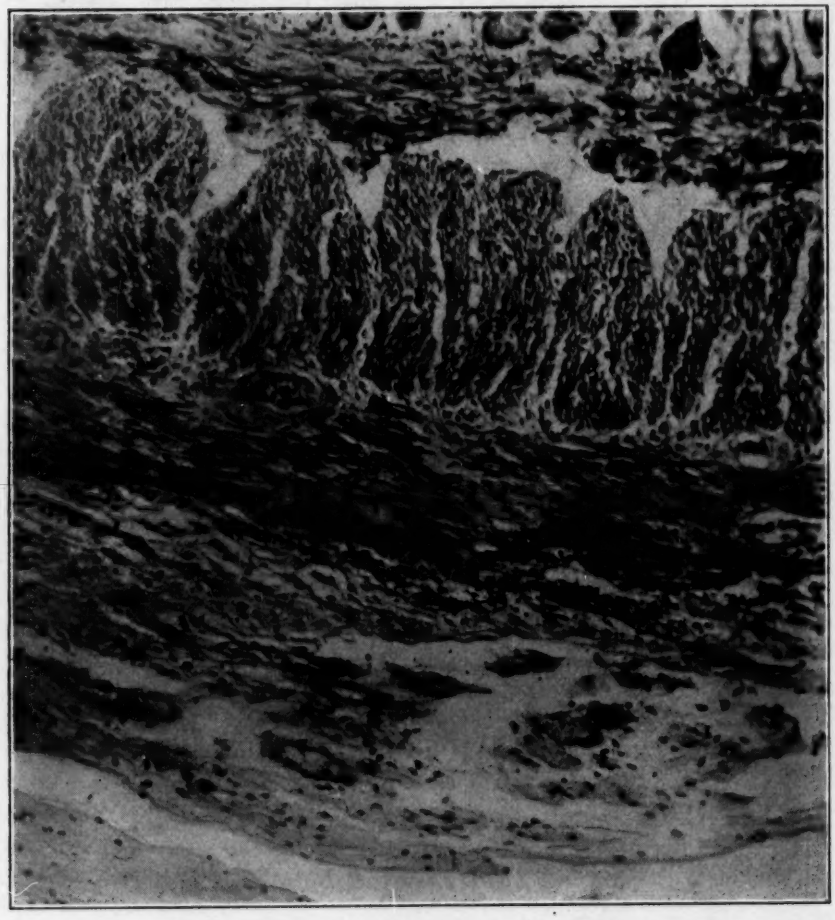

Fig. 4.—Photomicrograph of cross section through the wall of the small intestine, showing considerable thickening of the subserous layer caused by uniform proliferation of young fibroblastic cells with slight edema. Note that thickness of subserous coat is almost the same as that of the muscle coat.

thirty-first day in the hospital. On that evening, however, the patient had heart block, became listless and showed slight cyanosis. An electrocardiogram showed partial auriculoventricular 2:1 block; the auricular rate was 105 and the ventricular rate 52. Blood calcium was later reported as 16.1 mg. per hundred cubic centimeters. One and one-half hours later an electrocardio-

gram showed a P-R interval of 0.21, regular sinus rhythm and a prolonged Q-T interval.

On the thirty-second day in the hospital, blood calcium was 15 mg. per hundred cubic centimeters. Heart tones were good, and pulse rate normal, but the patient's color was poor and the lungs were full of rhonchi. Respirations became noisy, the pulse weak and the color worse, and the patient died.

Postmortem Observations (Dr. Kornel Terplan, University of Buffalo, Department of Pathology).—Postmortem cultures of peritoneal fluid and blood were sterile. From the postmortem urine were cultured colon bacilli which were resistant to more than 1,000 mg. of streptomycin per cubic centimeter of broth.

Autopsy showed pyelonephritis and ureteritis, especially pronounced on the left side, with notable dilatation of the left ureter. There was also diffuse interstitial nephritis of both kidneys. The gross and histologic picture showed progressive ascending purulent inflammation involving in diffuse fashion the entire kidney. Apart from the usual picture of inflammatory edema and more or less pronounced interstitial infiltrations, severe degenerative changes were present in the tubular system, especially in the proximal convolutions. All these changes represent various alterations usually seen in prolonged nephrosis.

The peritoneal cavity showed extensive thin adhesions. Microscopic section of the stomach showed extremely increased mucoid secretion, injection of capillaries in the mucosa and distinct hemorrhages. Various sections taken through the entire wall of the intestinal loops showed thickening of the subserous coat, caused by uniform proliferation of young fibroblasts, a moderate number of lymphocytes, few leukocytes and considerable edema. This edema extended somewhat into the muscle layer. There was no exudate on the surface. The appearance of the subserous and serous coats resembled that seen in ascites due to cirrhosis, except that the edema was more prominent and apparently more recent (fig. 4).

Distinct signs of rickets, which were not evident on roentgenograms, were noted along the costocartilaginous junction. These consisted of a broadened, irregular zone of the proliferating cartilage, a considerable amount of osteoid tissue, but only minimal thickening of the periosteum, especially at some distance from the cartilage. There was no fibrosis of the bone marrow.

There was evidence of generalized hydration. The brain showed slight edema and distinct hyperemia with injection of the meningeal veins. The liver was enlarged to about twice the normal size and showed fatty degeneration and subacute dystrophic changes.

COMMENT

It is evident that the use of artificial extrarenal pathways for the disposal of the metabolic end products can be entirely successful only in the presence of reversible renal lesions. Such lesions may include those resulting from acute nephritis, trauma to the urinary tract, toxic effects from heavy metals, blood transfusions or drugs, particularly sulfonamide compounds. In the patient reported on here, the renal lesion was acute pyelonephritis. The changes were reversible to the extent that following the peritoneal irrigation procedure the infant voided in amounts sufficient to return the elevated nonprotein nitrogen level of the blood to normal and to maintain her in good clinical condition for eight days.

The peritoneal irrigation procedure was successful in this case in that it tided the infant over the oliguric period by providing an excretory route for metabolic products, with the excretion of as much as 2.8 Gm. of urea nitrogen per day and a return of the blood nonprotein nitrogen level to normal. The peritoneal urea clearance of somewhat less than 4 cc. a minute is low compared with the normal of 20 cc. It represents, however, almost 20 per cent of the normal urinary urea clearance and, as Van Slyke and his associates [6] pointed out, is sufficient to prevent uremia. Correction for body surface gives a maximum value of 12.6 cc. per minute or close to the value of 15 cc. per minute which Fine and his co-workers observed to be adequate in the adult.

Evidence that the peritoneal irrigation procedure was not harmful is the fact that the patient lived for a period of eighteen days after the procedure was terminated. At postmortem examination, cultures of the peritoneal fluid were sterile and only thin adhesions were present in the peritoneal cavity. There was no evidence that the irrigation procedure was in any way responsible for the death of the patient. The two main factors responsible were the inability to control the infection of the kidney and the failure to maintain normal electrolyte and fluid balance after the peritoneal irrigation was discontinued.

Peritoneal irrigation, however, is a procedure to be used with caution. In addition to mechanical and technical problems, great difficulty was met in maintaining correct fluid and electrolyte balances. Undoubtedly, the greater lability of these balances in the infant makes the peritoneal irrigation procedure more hazardous than it is in the adult. Disturbance of acid-base balance, low blood sodium, potassium and phosphorus values and low and high levels of blood chloride and calcium were encountered during the course of illness. They were recognized by means of frequent blood chemical determinations and dealt with so far as possible by adjusting the composition of the fluids given orally and intravenously and of the irrigation fluid. As was suggested by others,[7] possibly less disturbance of the normal biochemical balance would result if the sodium, potassium and calcium in the irrigation solution were increased to approximate more closely the structure of normal blood plasma.

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6. Van Slyke, D. D., and others: Observations on the Courses of Different Types of Bright's Disease, and on the Resultant Changes in Renal Anatomy, Medicine **9**:257-386 (Sept.) 1930.

7. Seligman, A. M.; Frank, H. A., and Fine, J.: Treatment of Experimental Uremia by Means of Peritoneal Irrigation, J. Clin. Investigation **25**: 211-219 (March) 1946. Abbott, W. E., and Shea, P.: The Treatment of Temporary Renal Insufficiency (Uremia) by Peritoneal Lavage, Am. J. M. Sc. **211**:312-319 (March) 1946. Odel and Ferris.[3]

SUMMARY

A case of acute renal failure due to pyelonephritis in an 8 month old infant treated with peritoneal irrigation is presented. The apparatus used is described. It is concluded that peritoneal irrigation is a feasible procedure in an infant. Complete success of the procedure requires the presence of a reversible renal lesion and the ability to maintain a normal electrolyte and fluid balance. The latter is difficult and necessitates frequent blood chemical determinations for guidance.

Dr. Edward M. Bridge, Research Department, Children's Hospital, 219 Bryant Street (9).

Case Reports

POSTVACCINATION ENCEPHALITIS

A Problem in Differential Diagnosis

ALBERT P. ROSEN, M.D.
AND
RUDOLF A. JAWORSKI, M.D.
PROVIDENCE, R. I.

THE DIAGNOSIS of postvaccination encephalitis has posed a problem to the clinician ever since it was established as a definite clinical entity.

The program for large scale vaccination which took place in New York city during 1947 well illustrated the difficulties of attaining the correct diagnosis. More than 6,350,000 persons were vaccinated in a period of one month. Within two and one-half months after the vaccination program was instituted, 50 cases of possible encephalitis were reported to the department of health. Four of these cases were ruled out as definitely not encephalitis. In the remaining 46 cases, the diagnosis was considered probable. Death resulted in 8 of these cases. Brain tissue in each of the fatal cases was examined, and in none of them were the characteristic lesions of postvaccination encephalitis observed. Autopsy showed that 2 of the deaths were caused by tuberculous meningitis, 1 by brain tumor, 1 by coronary sclerosis and 4 probably by cerebral lesions.[1] The causes of illness in the remaining 38 cases remain in the realm of speculation.

The disease is rare in the United States. Approximately 85 cases have been reported in the American journals. The Charles V. Chapin Hospital contagion unit which serves Rhode Island has listed 1 case in 68,500 admissions since its inauguration thirty-eight years ago.

One factor lending to the confusion is the obscure origin. Several theories have been advanced, but none has been conclusive. The three most accepted hypotheses are that the disease is caused by an allergy,[2] by an activation of a latent virus and by the vaccine virus itself.[3]

The clinical course is rapid, with death or amelioration within one or two weeks. The fatality rate is high, but, when recovery does take place, it tends to be complete. The prodromal stage, which usually appears at the height of the vaccinia ten to thirteen days following vaccination, includes headache, vomiting, fever, drowsiness, nuchal rigidity and convulsions in children and infants. Adults and older children who

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From the pediatric service of Harold G. Calder, M.D., Charles V. Chapin Hospital.

1. Weinstein, P.: An Outbreak of Smallpox in New York City, Am. J. Pub. Health **37**:1376-1384 (Nov.) 1947.

2. Finley, K. H.: Pathogenesis of Encephalitis Occurring with Vaccination, Variola and Measles, Arch. Neurol. & Psychiat. **39**:1047-1054 (May) 1938.

3. Newman, S.: Postvaccinal Encephalitis, J. Pediat. **3**:461-470 (Sept.) 1933.

escape the intense manifestations show paralysis affecting one or more extremities, as well as those parts supplied by the cranial nerves, with involvement of the face, eyes and organs of speech and deglutition. Reflexes disappear and the Babinski sign is sometimes present. Often bladder and rectal functions are affected, leading to either incontinence or retention. The occasional occurrence of trismus has led to confusion with tetanus.[4]

The following case includes several of the diagnostic problems confronting the clinician.

REPORT OF A CASE

R. C., an 8 year old boy, was admitted to the Charles V. Chapin Hospital on June 28, 1947 because of stiffness of the back and difficulty in opening his mouth.

He was well until one day before his admission, at which time his mother noticed that he had some difficulty in opening his mouth. Ten hours before his admission, the boy complained of a stiff back. The difficulty with his mouth increased to the point where it could not be opened more than 1 cm. Speech and ability to swallow, however, were not impaired.

The child was vaccinated on the left arm June 17, eleven days prior to his admission, at which time a shield was placed over the site of vaccination; it was not removed, except for an occasional cleansing of the wound, until the day of his admission. A day before his admission, a purulent discharge developed at the vaccination site. He periodically complained of pain in the corresponding shoulder. The parents disclosed that the boy lived on a farm and drank well water which was located 30 feet (9 meters) from a cesspool.

The remainder of the history was noncontributory.

Physical examination revealed that the temperature was 100 F., pulse 120 and respirations 24. The child was well developed, well nourished and in pronounced opisthotonos with trismus of the jaw. He was alert and rational, spoke indistinctly and had a moderate amount of pain in the back which was accentuated by loud sounds. When the bed was jarred, he would have a momentary tonic spasm of his body. There were a few faded, red papules which were widely separated, and these were concentrated mainly on the abdomen. One of the lesions was crusted. The mother thought the cutaneous lesions developed about three days before his entry to the hospital. The pupils were small, regular and equal and reacted sluggishly to light. The mouth could be opened only slightly. There was extreme nuchal rigidity with hyperextension of the neck. The lungs were clear, but there were limited respiratory excursions. The abdominal muscles were spastic. The left arm had a deep, dirty vaccination ulcer which was about 2.5 cm. in diameter with considerable pus formation. The abdominal, deep tendon and achilles reflexes were not elicited. The Babinski and Kernig signs were absent. The lymph nodes, including those in the left axilla, were not enlarged.

Laboratory examination revealed the nose and throat cultures and the urine to be negative for pathogenic organisms. The white cell count was 14,500 leukocytes, of which 76 per cent were neutrophils; there was no shift to the left. The spinal fluid was normal. A direct smear of the wound failed to reveal any organisms. The anaerobic culture was negative, and the aerobic culture contained some weakly hemolytic Staphylococcus aureus.

4. Flexner, S.: Postvaccinal Encephalitis and Allied Conditions, J. A. M. A. **94**:305-311 (Feb. 1) 1930.

The diagnostic impressions at the time of his admission were bulbar poliomyelitis (there was an increased incidence of poliomyelitis in Rhode Island at the time of admission), postvaccination encephalitis and tetanus. Because of the absence of cells in the spinal fluid and the general clinical picture, tetanus was considered the most likely diagnosis.

The therapy included 50,000 units of tetanus antitoxin intravenously and 30,000 units intramuscularly; the periphery of the wound was infiltrated with 20,000 units. Large doses of barbiturates were utilized to control the spasms. The wound was cleaned with hydrogen peroxide and covered with sodium perborate paste. Intravenous administration of fluids was instituted, and 60,000 units of penicillin was given every three hours.

On the second day in the hospital the large doses of barbiturates were continued. The patient no longer became spastic with the slightest external stimuli. Only loud sounds or excessive handling provoked spasms. The trismus was slightly diminished. He continued to show improvement until that evening, when he had a severe generalized tonic spasm which included the intercostal muscles and led to respiratory arrest with subsequent cyanosis. Oxygen and artificial respiration were given. Calcium gluconate was given intravenously.

On the third day in the hospital, there were no convulsions. Vitamins and plasma were given intravenously, and large doses of barbiturates were continued.

On the fourth day, he had seven attacks of generalized spasticity, respiratory arrest and cyanosis, each one having a duration of about five to ten minutes. On each occasion, either a house officer or a nurse instituted artificial respiration until the normal respiratory rhythm returned. It was decided that the barbiturates were ineffective in controlling the convulsions, so they were discontinued.

The fifth day in the hospital showed little change.

On the sixth day, the patient still did not regain consciousness. Because of the poor response to what was considered adequate therapy for tetanus and failure to regain consciousness between spasms, a diagnosis of postvaccination encephalitis was considered.

Patient died on the seventh day in the hospital. A lumbar puncture was done immediately after death; the spinal fluid, as at the initial examination, was normal.

An autopsy was performed and the observations were consistent with postvaccination encephalitis. Gross examination of the brain showed the meningeal vessels to be heavily congested and prominent. The cerebral convolutions were noticeably flattened, with resultant narrowing of the intervening sulci. On section, the brain tissue throughout had an edematous appearance and the congested vessels were not emptied by scraping with the flat of a knife. Sections of the basal ganglions, midbrain, cerebellum, pons, medulla and spinal cord all presented the same congested, edematous appearance.

The microscopic picture demonstrated the pia-arachnoid of both brain and spinal cord to have greatly dilated and congested blood vessels, confirming the gross observations. Sections of the cerebral cortex, basal ganglions, cerebral peduncles, pons, cerebellar peduncles, medulla and spinal cord all showed extravasations of red blood cells in the perivascular spaces, in addition to the dilatation and congestion of the vessels. Numerous small, irregularly outlined foci of interstitial hemorrhage were seen throughout the spinal cord. The perivascular extravasations of red blood cells and interstitial hemorrhages were seen in both gray and white matter. An occasional blood vessel showed small numbers of lymphocytes in the adventitia or perivascular spaces. Small foci of gliosis

and neuronophagia with considerable numbers of endothelial cells were seen in different areas, especially in the regions surrounding the central canal of the spinal cord and the floor of the fourth ventricle. The ganglion cells in numerous areas showed chromatolysis, edema and displacement of the nuclei.

Sections of tissue taken through the vaccination scar demonstrated the surface to be covered with an eschar composed of granular cellular debris, masses of organisms and polymorphonuclear leukocytes. Proliferations of granulation tissue were seen beneath the eschar. These regions were extensively infiltrated with lymphocytes, polymorphonuclear leukocytes, eosinophils and a few mononuclear leukocytes.

In addition to the aforementioned observations, there was bilateral bronchopneumonia; toxic splenitis, hepatitis and lymphadenitis, generalized anasarca, pleural effusion and ascites were also present.

COMMENT

The diagnosis of postvaccination encephalitis can be difficult to establish ante mortem. Because of the paucity of cases in the United States, it may not be considered in the differential diagnoses. Armstrong [5] was of the opinion that it can be confused with tetanus, meningitis, epidemic or tuberculous types of encephalitis, encephalitis lethargica, poliomyelitis, sunstroke, cerebral hemorrhage, epilepsy and hysteria. Of these, tetanus is the most difficult to rule out when the spinal fluid contains a normal number of cells and trismus is present, because of the existence of the vaccination wound. An increase in spinal fluid cells eliminates tetanus but, unfortunately, not all cases have augmented cells.[6]

The difficulty has been well recognized. Newman [3] pointed out that, in the opinion of present authors, some cases of postvaccination encephalitis in the past were mistaken for tetanus. In Germany, an attempt has been made to reconstruct a great many such instances from the clinical and mortality records of vaccination cases.

Armstrong [5] laid great stress on consideration of the incubation period in establishing the diagnosis. An interval of fourteen days or less from vaccination to the onset of symptoms strongly favors postvaccination encephalitis, while one of seventeen days or longer favors tetanus.

We feel that any condition suspected to be tetanus following vaccination should be treated vigorously with tetanus antitoxin, sedatives and penicillin. However, if there is no response to adequate therapy, postvaccination encephalitis should be strongly considered.

SUMMARY

Tetanus and encephalitis may follow vaccination. Because postvaccination encephalitis is rare in the United States, it is frequently overlooked in the differential diagnosis. A case is presented that demonstrates some of the difficulties which the clinician encounters.

3-16 Kenneth Avenue, Fairlawn, N. J.

5. Armstrong, C.: Postvaccination Encephalitis with Special Reference to Prevention, Pub. Health Rep. **47**:1553-1568 (July 22) 1932.

6. Gorter, E.: Postvaccinal Encephalitis, J. A. M. A. **101**:1871-1874 (Dec. 9) 1933. Bauer, E. L.: Virus Encephalitis, J. Pediat. **6**:512-516 (April) 1935. Reisman, H. A., and Utz, D. W.: Postvaccinal Encephalitis: Report of Two Cases with Recovery, Arch. Pediat. **60**:201-207 (April) 1943.

AN UNUSUAL STRAIN OF PSEUDOMONAS AERUGINOSA

HOMER F. MARSH, Ph.D.
HENRY B. STRENGE, M.D.
AND
JAMES M. STEM, M.D.
OKLAHOMA CITY

INFECTIONS in the newborn due to Pseudomonas aeruginosa (Bacillus pyocyaneus) are well recognized, yet surprisingly few cases are reported. The organism is presumably highly virulent for the newborn, infections usually being fatal if generalized sepsis occurs. According to Schultz,[1] the septic state is characterized by a tendency to hemorrhage and diarrhea.

An idea of the incidence of septicemia caused by this organism may be gained from the report of Dunham [2] who studied 39 cases of septicemia in the newborn and found only 1 case caused by Ps. aeruginosa. More recently, Kerby [3] reviewed the literature and reported 39 cases of Ps. aeruginosa septicemia in children. He concluded from his study that the source of the organism in many cases was the gastrointestinal tract.

Reports of this organism's isolation in other infections, such as meningitis, endocarditis and diarrhea, are to be found.[4]

The 2 cases reported here seem to be of general interest because of the nature of the infections, which were pneumonia, stomatitis and rhinitis in one case and meningitis in the other, and of particular interest because

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From the Department of Bacteriology and the Department of Pediatrics of the University of Oklahoma School of Medicine.

1. Schultz, F. W., in Brennemann, J.: Practice of Pediatrics, Hagerstown, Md., W. F. Prior Company, Inc., 1945, vol. 2, chap. 24, p. 12.

2. Dunham, E. C.: Septicemia in New-Born, Am. J. Dis. Child. **45**:229 (Feb.) 1933.

3. Kerby, G. P.: Pseudomonas Aeruginosa Bacteremia: Summary of Literature, with Report of Case, Am. J. Dis. Child. **74**:610 (Nov.) 1947.

4. (*a*) Kraus, E. J., and Hunter, M. P.: Congenital Bacillus Pyocyaneus Infection, Arch. Path. **31**:819 (June) 1941. (*b*) Kerman, W. Z.; Perlstein, M. A., and Levinson, A.: Bacillus Pyocyaneus Meningitis Following Pneumoencephalography, Am. J. Dis. Child. **65**:912 (June) 1943. (*c*) Allin, A. E.: Meningitis of New-Born Due to Pseudomonas Aeruginosa, Canad. M. A. J. **44**:288, 1941. (*d*) Cooley, T. B.: An Epidemic of Infant Diarrhea, Apparently Caused by the Bacillus Pyocyaneus, J. A. M. A. **50**:607 (Feb. 22) 1908. (*e*) Moragues, V., and Anderson, W. A. D.: Endocarditis Due to Pseudomonas Aeruginosa, Ann. Int. Med. **19**:146, 1943. (*f*) Hunter, C. A., and Ensign, P. R.: An Epidemic of Diarrhea in a New-Born Nursery Caused by Pseudomonas Aeruginosa, Am. J. Pub. Health **37**:1166, 1947.

of the characteristics of the organism isolated from each case. The strain of organism isolated did not correspond to the usual description of Ps. aeruginosa in that it was encapsulated and grew in mucoid colonies.

Sonnenschein [5] was probably the first to describe the encapsulated strain of Ps. aeruginosa, having isolated such from a patient with typhoid cholecystitis while he was receiving antityphoid bacteriophage therapy. Sonnenschein was of the opinion that the strain isolated was a variant induced by the action of the bacteriophage and mentioned the work of others who had induced variation of Escherichia coli and the paratyphoid organisms through the action of bacteriophages. Schwarz and Lazarus [6] more recently reported the isolation of encapsulated strains of Ps. aeruginosa from urines of patients with various urinary tract infections.

REPORT OF CASES

Case 1 is reported in more detail than is case 2, but the characteristics of the organism isolated in each case were essentially the same.

CASE 1.—Baby C. was admitted to the hospital at the age of 2 days with a history of having vomited all feedings since they were begun at twelve hours, the presence of a yellowish membrane on the oral surfaces and a rattling sound during respiration.

Physical Examination.—On admission, the patient was observed to be acutely ill, cyanotic and having extreme difficulty in breathing. The membranes of the pharynx and tongue were patchily coated with a yellow membrane which caused no bleeding when removed. There was a yellow purulent discharge from the nose. Numerous harsh rhonchi and coarse moist rales were heard over the entire chest area, and breath sounds were of the bronchovesicular or bronchial type. Except for the temperature of 103.8 F., results of the rest of the examination were normal.

The diagnosis on admission to the hospital was pneumonia, stomatitis and rhinitis of undetermined cause.

Laboratory Data.—The hemoglobin content of the blood was 16 Gm.; the red blood cell count was 6,300,000, and the white cell count was 17,950, with a predominance of neutrophils. Repeated blood counts over several days revealed the expected physiologic decrease in hemoglobin content and red cells, but the leukocytosis persisted. At two weeks, the white cell count was 17,400, with 75 per cent neutrophils. The reaction to the Mazzini test was negative and a urinalysis revealed no abnormality.

Roentgenograms of the chest were made on the second day and were essentially normal in appearance, but plates made on the fourth day showed some infiltration of both subapical areas and gave an impression of bilateral pneumonia, probably of the aspiration type.

Smears made from material from the mouth and throat, when stained, showed the predominant presence of a gram-negative bacillus. Cultures made at varying intervals from the throat resulted in the recovery of pure growths of Ps. aeruginosa.

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5. Sonnenschein, C.: Die Mucosus-Form des Pyocyaneus-Bakteriums, Bakterium pyocyaneum mucosum, Centralbl. f. Bakteriol. (Abt. 1) **104**:365 (Oct. 31) 1927.

6. Schwarz, L. H., and Lazarus, J. A.: An Unusual Strain of Pseudomonas Aeruginosa, J. Bact. **54**:30, 1947.

On the twenty-first day in the hospital a culture was made but a coagulase-positive Staphylococcus aureus was the only organism present.

Description of the Organism.—Blood agar plates were inoculated with the specimen, and, after incubation, colonies of a heavy mucoid character not unlike those of Klebsiella pneumoniae were seen. Gram-stained preparations from these colonies, however, revealed a gram-negative bacillus which was heavily encapsulated but which was more slender than K. pneumoniae. India ink preparations from the colonies verified the presence of capsules on the organism.

Various carbohydrate broths and other differential mediums were inoculated from the colonies on the blood agar. Within twenty-four hours, only the dextrose preparation of the carbohydrate broths inoculated was fermented and this with the production of a small amount of acid and no gas. Litmus milk was alkaline and peptonization had begun. Nitrates were reduced, but indole was not formed. Gelatin was rapidly liquefied, as was coagulated serum medium. When the organism was tested from a three hour broth culture, it was observed to be actively motile. Examination of proteose peptone no. 3–dextrose agar slopes showed some soluble blue-green pigment, although the pigmentation was not as intense as that exhibited by several stock strains of Ps. aeruginosa on the same medium.

From the reactions observed, it could only be concluded that the organism was an encapsulated strain of Ps. aeruginosa.

Resistance of the Organism to Chemotherapeutic Agents.—In view of the therapy which had been initiated in this case, penicillin, sulfadiazine and streptomycin being used at various times, it was decided to test the action of these agents on the organism in vitro. This was done by using a culture of the organism only three transplants removed from the originally isolated colony and testing by the agar cup-plate method. The organism was observed to be insensitive to the action of as much as 10 units of penicillin per 0.1 cc.; 10 mg. of sulfadiazine per 0.1 cc. barely inhibited growth, and 50 units of streptomycin per 0.1 cc. had no effect on the growth. The last observation is in accord with that of Schwarz and Lazarus,[6] who reported that the strains isolated by them were resistant to the action of streptomycin.

Virulence Test.—At the request of Dr. Schwarz, a culture of this organism was sent to him for comparison with those strains which had been isolated by him. He compared it culturally and set up a virulence test. Three cubic centimeters of a broth suspension of the organism was washed in saline solution, and the suspended organisms were injected by the intravenous route into a 12 pound (5.4 Kg.) rabbit. Within one and one-half hours the animal showed definite respiratory symptoms. In three and three-quarter hours, the animal was comatose and there was some paralysis of the hindlimbs. In eight and one-half hours, the animal died. Diagnosis at postmortem examination was pneumonia and possible meningitis.

CASE 2.—Baby S. was admitted to the hospital at the age of 6 months, with the chief complaints of fever and convulsions. One week prior to admission, the patient had a cold, which progressed for about four days with the infant becoming lethargic and feverish. Two days before admission, a local physician had seen the patient and treated him, but during the night the patient "would not move." One day previous to his admission, he had a jacksonian type convulsion localized to the left arm and leg.

Physical Examination.—On his admission, the patient was acutely ill and somewhat lethargic, and the skin was hot and dry. The temperature was 104.8 F.

The anterior fontanel was bulging, the neck was rigid, and the right tympanic membrane was injected and bulging. Tachycardia was evident. Neurologic examination revealed active tendon reflexes and the presence of Kernig and Brudzinski signs.

The diagnosis on his admission was acute meningitis and otitis media on the right side.

Laboratory Data.—Examination of the spinal fluid on admission revealed gram-positive diplococci. Cultures of the spinal fluid confirmed the identity of the organism as Diplococcus pneumoniae, type 23.

Course in the Hospital.—Although penicillin and sulfadiazine were administered parenterally in large doses and penicillin was given intrathecally, response was slow and the patient continued to show some clonic convulsions. On the eighth day it was decided to discontinue the penicillin intrathecally. The patient was unresponsive to any stimuli except pain, and it was felt that extensive damage to the brain had resulted from the infection. A clinical recurrence of meningitis followed the withdrawal of penicillin, but resumption of therapy resulted in improvement. Administration of sulfadiazine was discontinued at this time.

Within a few days, the temperature began to rise and a culture made from the spinal fluid showed the presence of an organism having the same cultural characteristics as that isolated from case 1, namely, encapsulated Ps. aeruginosa.

Streptomycin was given intrathecally, but no improvement resulted and the patient died on the twentieth day of hospitalization.

Postmortem examination confirmed the diagnosis of meningitis and, although no cultures were made at this time, it was remarked that the meninges were greenish in appearance and seemed to be of a gelatinous consistency.

COMMENT

Possible Source of Infection.—One finds suggestions concerning the possible source of Ps. aeruginosa in infections, and we feel that in one of these cases the source may be clearly indicated. In the other, there was some indication but no definite proof of the manner in which the organism may have been introduced. It is regrettable that an opportunity was not available for further study in this regard in the case of baby C.

Baby C. was born in a small hospital in another part of the state and was brought to the Crippled Children's Hospital the day after birth. On admission, it was learned that another infant born in the same hospital as baby C. had died after a brief illness. This illness was described as being similar to that of baby C. Stomatitis had been observed and, although no cultures had been made, direct smears from the lesions indicated the presence of gram-negative bacilli.

A nurse in the same hospital had been ill at about the same time that the first baby died. She had also complained of stomatitis but no cultures were made.

In the case of baby S., we are reminded of the conclusions of Kerman and his associates [4b] who investigated the occurrence of Ps. aeruginosa in cases of meningitis and held the opinion that in the majority of cases such infections were complications of lumbar puncture or the manipulations of pneumoencephalographic study. Baby S. was certainly admitted to the hospital with D. pneumoniae meningitis, and it must be

presumed that, during manipulations of lumbar puncture for the administration of penicillin, Ps. aeruginosa must have been introduced.

Serologic Response of Baby C.—Serologic tests for the presence of agglutinins in the serum of baby C. were set up in an effort to associate the Ps. aeruginosa more closely with the actual infection. Two different tests were performed one month apart, but agglutinins above a titer of 1 : 10 could not be demonstrated. This was disconcerting in view of the observations of Schwarz and Lazarus,[6] who reported that serums from their patients agglutinated Ps. aeruginosa in a 1 : 5120 dilution. In considering the respective ages of the patients, however, we feel that the lack of response on the part of baby C. does not vitiate the probability that Ps. aeruginosa was actually the infecting organism. It is doubted that Baby G. was old enough to produce antibodies against any antigen.

Therapy.—Therapy in the case of baby C. is interesting in view of the in vitro observations regarding the resistance of the organism to penicillin and streptomycin. It was somewhat inhibited in growth by sulfadiazine, and this substance, administered parenterally and used locally in 25 per cent solution as a spray to the throat, resulted in clearing of the throat and decided improvement of the condition within four days.

In the study of the organism isolated from baby S., it was observed that its resistance to streptomycin was not as definite as that of the organism isolated from baby C. The second organism, that from baby S., was inhibited in its growth by 6 units of streptomycin per 0.1 cc. This was not discovered until the death of baby S., however, and, although streptomycin had been administered after the organism was discovered in the spinal fluid, it is now believed that the disease was too far advanced for the patient to have benefited by the streptomycin.

SUMMARY

Two cases are described in which Pseudomonas aeruginosa was the infecting organism, causing pneumonia, stomatitis and rhinitis in one case and meningitis in the other.

Cultural characteristics of the organism correspond to those of stock cultures of the same organism, except for the fact that the organism from the cases described was encapsulated and grew in mucoid colonies.

801 Northeast Thirteenth Street.

AVITAMINOSIS A IN GIARDIASIS

PETER V. VÉGHELYI
AND
FRANCIS J. LÁNCOS
BUDAPEST, HUNGARY

IT HAS been repeatedly stated that severe infection with the protozoon Giardia lamblia acting as a barrier to absorption from the intestine often leads to celiac symptoms.[1] This view has been widely accepted and several times confirmed in pediatric literature, especially since there is experimental evidence that the absorption of vitamin A is intensely disturbed in these cases.[2] Cases of grave vitamin deficiency are, however, rare. This is the reason that, besides emphasizing the pathologic importance of giardiasis, the following case seemed of interest.

REPORT OF CASE

B. R., a male child 28 months of age, was admitted to the hospital with keratomalacia of both eyes. He was emaciated, weighing 6,600 Gm., and had had offensive loose stools for a year. The history was irrelevant except that he came from a country where hypovitaminoses A are almost nonexistent and that both his brothers, fed on the same diet, with adequate vitamin A content, as he was, were healthy and well developed.

Nothing abnormal was found on physical examination, apart from the typical keratomalacia (fig. 1). Parasitologic examination revealed Giardia in the feces. Tests disclosed severe steatorrhea, unimpaired pancreatic function, hypochromic anemia and low vitamin A content in the blood (28 international units per hundred cubic centimeters), which rose to normal (92 international units per hundred cubic centimeters) after two injections of 50,000 international units of vitamin A.

Several tests were made in order to estimate the absorption capacity of the intestine. The curves obtained on both the vitamin A absorption test and the double dextrose tolerance test revealed an exceptionally poor absorption of these materials (fig. 2 and 3).

In treatment the patient was given 0.06 Gm. of quinacrine hydrochloride twice daily for five successive days and a week later, as cysts were still present in the feces, another similar course, following which parasites could never again be demonstrated. No other treatment was given and the child was kept on a normal diet. He gained rapidly in weight.

A week after the second treatment both the consistency and the fat content of the stools were normal, the double dextrose tolerance test yielded a physiologic

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From the 1st Department of Pediatrics of the Hungarian Petrus Pázmány University.

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2. Katsampes, C. P.; McCoord, A. B., and Phillips, W. A.: Vitamin A Absorption Test in Cases of Giardiasis, Am. J. Dis. Child. **67**:189 (March) 1944.

Fig. 1.—Typical keratomalacia in 28 month old child with avitaminosis A due to giardiasis.

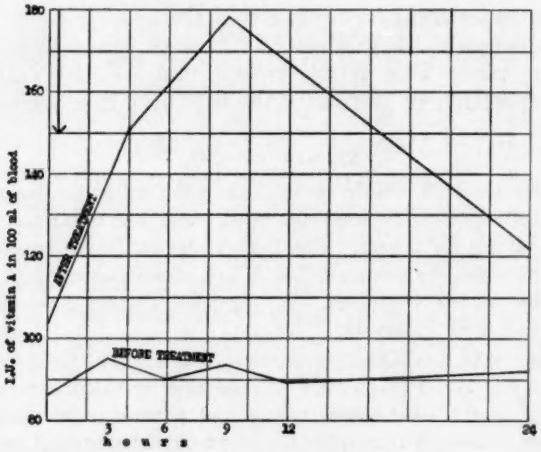

Fig. 2.—Graph showing results of vitamin A absorption test.

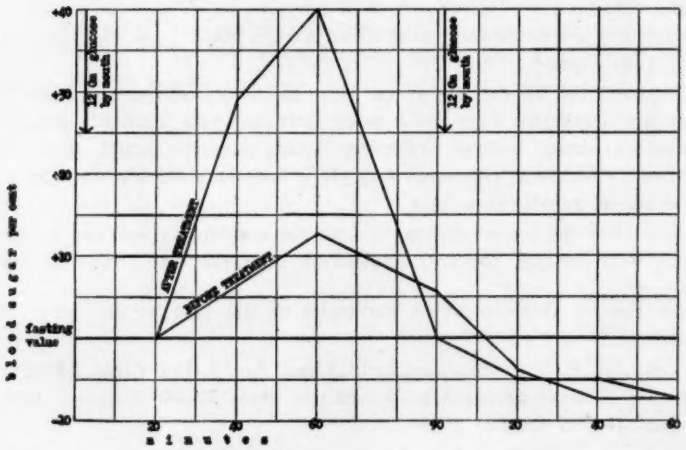

Fig. 3.—Graph showing results of double dextrose tolerance test.

curve and a positive Exton-Rose effect and the curve for vitamin A absorption was also normal. Three weeks later the weight was 10,300 Gm., the vitamin A content of the blood normal and the anemia almost healed (figs. 2 and 3).

The conclusion which may be drawn from this case is that infection with Giardia must be considered pathogenic in every instance and that

Data on Patient with Avitaminosis A Due to Giardiasis

	Before Treatment	After Treatment
Weight	6,600 Gm.	10,300 Gm.
Fat in dry substance of feces	46%	9%
Hemoglobin concentration	48%	78%
Red blood cell count	2,800,000	4,180,000
Vitamin A in blood (per 100 cc.)	28 I. U.	104 I. U.

Fig. 4.—The patient before and after treatment.

in cases of unexplained deficiencies of fat-soluble vitamins investigation to determine the presence of a protozoan infection is always indicated.

SUMMARY

A child 28 months of age with keratomalacia of both eyes was demonstrated to harbor Giardia lamblia. He had steatorrhea, hypochromic anemia and low vitamin A content in the blood. The curves for both vitamin A absorption and dextrose tolerance showed exceptionally poor absorption of these materials.

After the parasite had been eradicated, the absorption of both vitamin A and dextrose became normal, the excess fat disappeared from the feces, the patient gained much weight and his anemia greatly improved.

Bokay Janos u 53 (8).

Progress in Pediatrics

CUSHING'S SYNDROME DUE TO TUMOR OF ADRENAL CORTEX

Report of a Case of An Eleven Month Old Infant, with Apparent Operative Cure

HAROLD M. GOLDSTEIN, M.D.
NEW YORK

DISEASES of the adrenal cortex have attracted widespread attention in the medical literature since ancient times because of the dramatic character of the clinical syndromes they produce. The adrenocortical syndrome has been frequently reviewed (Bulloch and Sequeira, 1905; Glynn, 1911-1912; Haymaker and Anderson, 1938; Reilly, Lisser and Hinman, 1939; Marks, Thomas and Warkany, 1940; Farber, Gustina and Postoloff, 1943; Goldstein, Rubin and Askin, 1946; Wilkins, 1948). In children, the clinical manifestations of hyperfunction of the adrenal cortex vary with the age and sex of the patient, as well as with the hormonal production of the hyperfunctioning cells. Prenatally, hyperplasia of the adrenal cortex may cause virilization of the external genitalia of female infants or female pseudohermaphrodism (Young, 1937). This condition is compatible with a normal, although sometimes confused, lifespan. In rare instances female pseudohermaphrodism may be associated with an adrenocortical tumor (Krabbe, 1921; Scabell, 1925). The metabolic changes of Cushing's syndrome have not been reported in connection with this group of cases. However, cases of neonatal or infantile adrenocortical insufficiency, or Addison's disease, have been described in association with hyperplasia of the adrenal cortex. This may be associated in the male infant with virilization and in the female infant with pseudohermaphrodism (Thelander and Cholffin, 1941; Wilkins and others, 1940; Bratrud and Thompson, 1943; Jaudon, 1946).

In infants and young children before puberty the term "adrenogenital syndrome" best describes those disorders in which the biologic effects of increased production of androgenic hormone alone are apparent. In female children with this syndrome one notes hirsutism of the face and limbs, pseudosexual precocity with enlargement of the labia and clitoris, deepening of the voice, a temporary increase in "bone age" and rapid growth, followed by early closure of the epiphyses. The size of the uterus is either normal or small and menstruation usually does not occur, even in older children who have reached the age of puberty. Several exceptional instances of pre-

From the Department of Pediatrics, Mount Sinai Hospital.

cocious menstruation have been reported (Walters and others, 1934). In the male child rapid growth, increased muscular development, extensive hirsutism of face and pubis, and frequently the entire body, and precocious sexual development with increase in size of the external genitalia have been described. Spermatogenesis rarely occurs. Only 1 case has been reported of a male child with a tumor of the adrenal cortex producing feminization with enlargement of the breasts (Wilkins, 1948). In children of either sex with the adrenogenital syndrome, tumors of the adrenal cortex, frequently malignant, have been more frequently encountered than adrenocortical hyperplasia (Goldstein and others, 1946).

The metabolic disturbances of Cushing's syndrome in children may be associated with the adrenogenital, or virilizing, syndrome or may occur in almost pure form with slight virilization. The symptom complex described by Cushing (1932 *a*) is characterized by rapidly progressive obesity, chiefly involving the face, neck and trunk, osteoporosis, purplish striae of the skin, polycythemia, acne, cyanosis and purpura, alterations in carbohydrate metabolism (occasionally, frank diabetes mellitus resistant to insulin therapy), hypertension and, at times, severe asthenia, polydipsia, polyuria and polyphagia. In 1940, Marks, Thomas and Warkany collected 23 cases of adrenocortical obesity, with other manifestations of Cushing's syndrome, in children before puberty and added a case of their own. Additional cases of Cushing's syndrome due to adrenal pathologic changes in children have been reported since by Gross (1940), McQuarrie (1944), Friedgood and Gargill (1938) and Neff and others (1942). To this list we wish to add a case of Cushing's syndrome in a young infant observed by us.

REPORT OF CASE

History.—K. M., an 11 month old white, female infant, was admitted to the pediatric service of the Mount Sinai Hospital on May 6, 1947 because of hirsutism and obesity. The family history was not remarkable. Birth was normal and weight at birth was 10 pounds 5 ounces (4,678 Gm.). At the age of 3 months a minimal amount of fine hair was noted on the child's back, face and pubis. This was not considered abnormal until one month preceding her admission when the growth of hair progressed more rapidly. By the end of the fifth month the infant had doubled her weight at birth. The feeding history was not remarkable. At the age of 7 months the parents became impressed with an unusual fulness of the child's face. From that time obesity had been rapidly progressive, the fat being deposited successively on the face, neck, proximal extremities and trunk. The child was a pleasant, active infant whose development had been entirely normal except that she could not achieve the sitting position unaided. She had had intercurrent infections of the upper respiratory tract and bouts of purulent otitis media at 8 months and again at 10 months of age but had enjoyed apparent good health otherwise. No cutaneous abnormalities had been noted. The voice was not considered altered. For several months preceding her admission the child's physician had recorded

failure to gain normally in height and weight. The remainder of the history was noncontributory.

Physical Examination.—On her admission her temperature was 99.4 F.; the pulse rate was 128 per minute and the respiratory rate, 32. The blood pressure was 230 systolic and 140 diastolic.

The child was seen to be remarkably obese (fig. 1). The face, neck, trunk and proximal extremities were particularly involved; however, the abdomen and the distal extremities also showed excessive fatty deposition. Her height was 28 inches (71 cm.) and her weight was 22 pounds 12 ounces (10.3 Kg.). Facial obesity was so pronounced as to give the appearance of a "moon face." Hirsutism, involving

Fig. 1.—The patient's clinical appearance on admission. The obesity is well demonstrated. Unfortunately, the plethoric cheeks and hirsutism of face and trunk are not apparent.

the dorsum of the trunk, pubis and sides of the face, was prominent. The child appeared neither acutely nor chronically ill and exhibited normal interest in her surroundings. She sat up normally only when raised and did not stand. The skull was normal; the anterior fontanel was 3 cm. in diameter and was not tense. Examination of the eyes, including funduscopy, showed nothing unusual. Ears, nose, mouth and throat appeared normal except for an intensely reddened pharynx. The dentition was normal. The tongue was frequently protruded but did not seem enlarged. The cheeks appeared plethoric and several spider telangiectases were present. The neck was supple and the trachea was in the midline. The heart did

not appear enlarged. The heart sounds were of good quality and there were no murmurs or thrills. The lungs were clear to percussion and auscultation. The abdomen was not distended. The liver and spleen were not enlarged. In the left flank a firm, smooth, rounded mass was palpated 5 cm. below the costal margin. Examination of the skeleton and extremities revealed poor tone of the musculature and the obesity described previously. Neurologic examination showed no abnormality. The genitalia were normal except for slight enlargement of the clitoris. No pelvic organs could be palpated on combined rectal and abdominal examination. The voice was normal. No striae atrophicae, purpura or acne was noted.

Laboratory Findings.—Laboratory studies on the patient's admission revealed a hemoglobin concentration of 16.3 Gm., a red blood cell count of 4,500,000 and a white blood cell count of 12,300, with a normal differential count. The urine had a specific gravity of 1.024 and was otherwise normal. No glycosuria or albuminuria was noted. The hematocrit reading was 50 per cent and the sedimentation rate was 17 mm. per hour (Westergren). Results of blood chemical studies were as follows: Urea nitrogen was 16 mg. and total serum protein 6.3 Gm. per hundred cubic centimeters. Sodium was 150.9 and potassium 5.6 milliequivalents per liter. Oral ingestion of 1.75 Gm. of dextrose per kilogram revealed decreased dextrose tolerance: the level on fasting was 80 mg.; at one-half hour, 170 mg.; at 1 hour, 200 mg.; at 2 hours, 170 mg., and at 3 hours, 80 mg. per hundred cubic centimeters. The tourniquet test gave a negative result. The twenty-four hour urinary excretion of 17-ketosteroids was 4.0 mg. in a total urinary volume of 175 cc. The electrocardiogram showed sinus tachycardia, unusual axis deviation and diphasic, high voltage QRS complexes in all leads, but no abnormality to indicate myocardial involvement. The roentgenograms of the skull and long bones showed no abnormalities: the sella turcica was normal, and there was no distinct osteoporosis. The roentgenogram of the chest showed the heart to be the upper limit of normal in size and the lungs to be normal. A flat plate of the abdomen and intravenous urography failed to reveal any significant abnormality. Combined intravenous urography and sectional roentgenography was performed. By this method a mass was demonstrated in the right suprarenal area displacing the kidney caudad (fig. 2). Perirenal insufflation was next attempted on the right side but was unsuccessful. While the patient was under general anesthesia for this procedure, a mass was palpated in the right flank for the first time.

Diagnosis.—The combination of hirsutism, plethora, pronounced obesity, hypertension and decreased dextrose tolerance indicated the diagnosis of Cushing's syndrome. The increased urinary excretion of 17-ketosteroids supported this diagnosis and indicated underlying pathologic changes in the adrenal gland. The mass palpable in the left flank on admission was at first thought to be related to a left-sided adrenocortical neoplasm. However, the demonstration of a tumor in the right suprarenal region by combined intravenous urography and sectional roentgenography indicated the presumptive diagnosis of an adrenal tumor on the right side.

Course in the Hospital.—Urologic consultation was obtained and exploration of the right suprarenal region was advised. While preparations for operation were in progress, the child suddenly became febrile and refused feedings. She was discovered to have acute pharyngitis and bilateral acute otitis media and subsequently had severe parenteral diarrhea. Nasopharyngeal culture yielded a pure growth of Staphylococcus aureus A which was ten times as resistant as the standard organism to penicillin and was 50 per cent inhibited by 10 mg. per hun-

dred cubic centimeters of sulfadiazine. Culture of the stool revealed no pathogens. A period of starvation was followed by small, graduated feedings of skimmed milk, and parenteral administration of fluids was started. Penicillin was given intramuscularly every three hours and sulfadiazine was given by mouth. After two weeks of treatment, the respiratory infection and diarrhea were finally brought under satisfactory control. This had hardly been accomplished when, during the hot summer weather, the child acquired a pustular, acneform infection superimposed on a widespread sudamina. The latter infection occurred while the patient was still receiving penicillin intramuscularly. This infection was associated with a sharp febrile rise and leukocytosis and was observed on culture to be due to hemolytic Staph. aureus A. This organism was demonstrated to be fifteen times as resistant as the standard organism to penicillin, one time as resistant as the standard organism to streptomycin and 50 per cent inhibited by 10 mg. per hundred

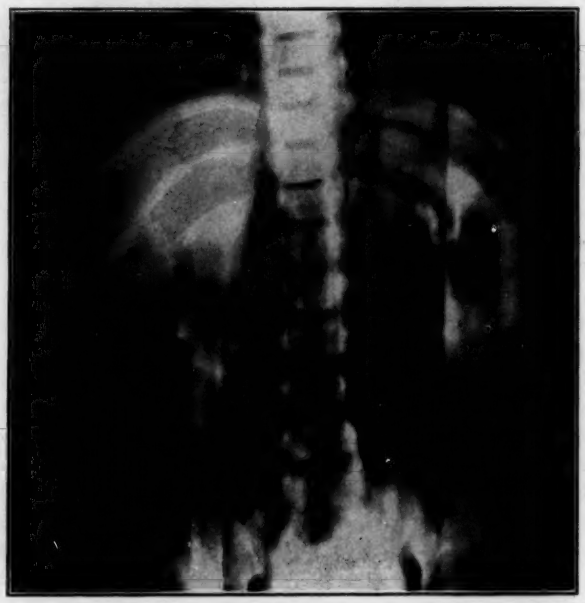

Fig. 2.—Sectional roentgenogram (laminagram, tomogram) of abdomen as performed following injection of iodopyracet. Oblique arrows delimit the right suprarenal tumor mass. Vertical arrows indicate the lower border of both kidneys. The right kidney is seen to be displaced caudad by the tumor mass.

cubic centimeters of sulfadiazine. Use of penicillin was discontinued and 0.1 Gm. (100,000 units) of streptomycin was given every three hours intramuscularly in addition to local treatment. This regimen controlled the cutaneous infection sufficiently well to permit surgical exploration.

Operation.—It was decided to utilize the following therapeutic agents: Five per cent dextrose in isotonic sodium chloride solution intravenously, whole blood transfusions, whole aqueous adrenal cortex extract, adrenal cortex extract (hog) and epinephrine (adrenalin®) if the blood pressure were to fall precipitously. The adrenal cortex extract (hog) contains several carbohydrate factors lacking in the whole aqueous adrenal cortex extract and the combination of both preparations was thought to provide more adequate replacement therapy. It was decided not

to employ desoxycorticosterone, since overdosage with this drug, especially in the presence of adrenocortical insufficiency, may result in edema, hypertension and possible cardiac failure.

The following detailed schedule of treatment was adopted, beginning on the day of operation:

9 a. m.: 10 cc. whole aqueous adrenal cortex extract subcutaneously
2 cc. adrenal cortex extract (hog) intramuscularly
Continuous intravenous administration of 5 per cent dextrose in isotonic sodium chloride solution

2 p. m.: 10 cc. whole aqueous adrenal cortex extract intravenously
10 cc. whole aqueous adrenal cortex extract subcutaneously
2 cc. adrenal cortex extract (hog) intramuscularly

On operation: Whole blood transfusions
5 to 10 cc. whole aqueous adrenal cortex extract intravenously every hour as indicated
Epinephrine, as needed

After operation: 2 cc. whole aqueous adrenal cortex extract every hour subcutaneously
1 cc. adrenal cortex extract (hog) every four hours intramuscularly
Continuous intravenous administration of 5 per cent dextrose in isotonic sodium chloride solution
Whole blood transfusion, as indicated

Operation was performed on the right side with the patient under anesthesia induced by the open drop ether method, utilizing a lumbodorsal approach. A well encapsulated suprarenal tumor was visualized and was easily enucleated by blunt dissection. A small section of apparently normal adrenal gland on the same side was taken for biopsy prior to closing the wound. No evidence of regional metastases was observed.

Pathologic Examination.—The tumor was ovoid and weighed 30 Gm. It measured 4.5 by 4 by 3 cm. It was completely encapsulated. The consistency was moderately firm and somewhat fleshy. The cut surface showed a glistening, rather cellular, tissue which was dull tan. Throughout the tumor tissue there were irregular flecks and strands of bright yellow, most abundant under the capsule. No distinct fibrous stroma and no striking vascularity were evident. Microscopic examination revealed occasional mitotic figures, and the pathologic diagnosis of carcinoma of the adrenal cortex was made (fig. 3).

Postoperative Course.—The patient tolerated the operative procedure well with maintenance of blood pressure at a level of 200 systolic and 120 diastolic. Eighteen hours after operation the temperature rose sharply to 105.6 F. Blood pressure at this time was 180 systolic and 96 diastolic. The hyperpyrexia responded temporarily to tepid sponging and administration of salicylates. Twenty-four hours after the operation the child appeared apathetic and showed an ashen gray pallor. Hyperpyrexia recurred; the pulse rate ranged from 180 to 200 a minute and the blood pressure fell precipitously to 120 systolic and 80 diastolic.

Throughout this period the child continued to receive fluids by continuous intravenous administration and regularly scheduled doses of whole aqueous adrenal cortex extract and adrenal extract (hog) as previously described. Administration of penicillin and streptomycin in divided doses every three hours intramuscularly was continued. The child was placed in an oxygen tent.

Thirty-six hours after operation the patient's clinical condition appeared to be stabilized. The temperature had fallen from 105.6 to 101 F., the pulse rate from

200 to 138 per minute and blood pressure from 200 to 120 systolic and from 120 to 84 diastolic. The clinical appearance was improved. The child began to take fluids well by mouth. She was comfortable out of the oxygen tent. At this time

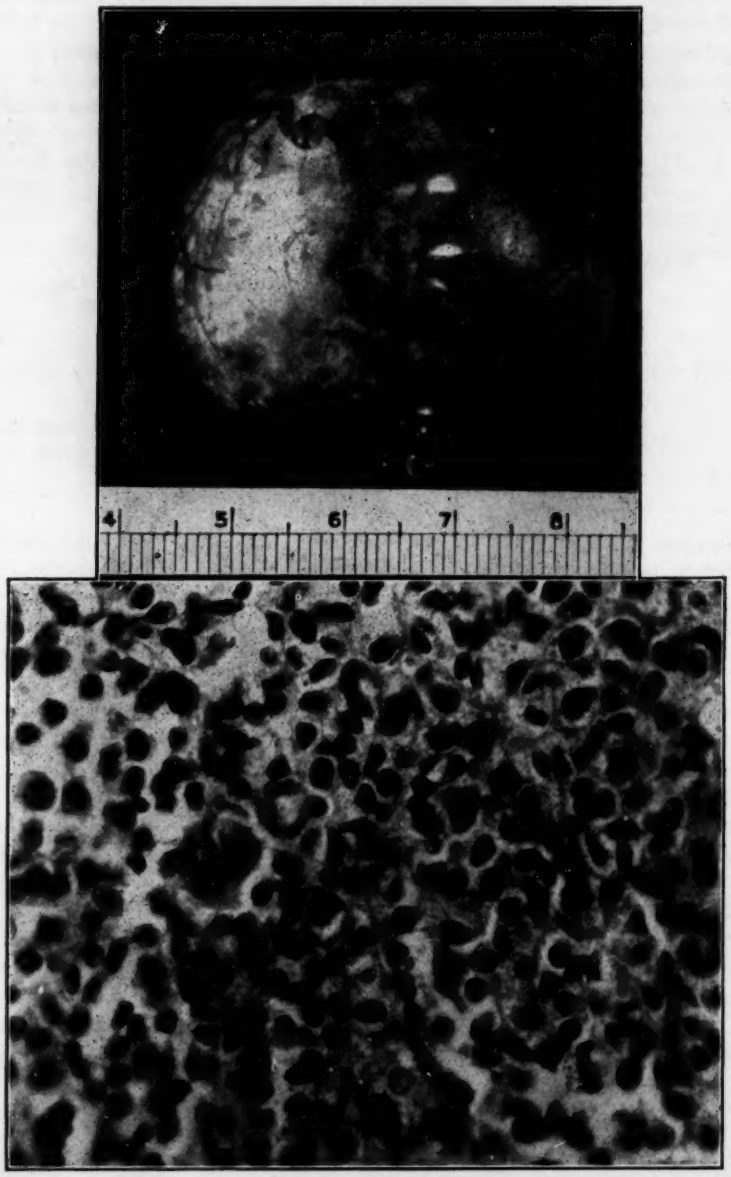

Fig. 3.—The upper portion demonstrates the gross appearance of the tumor. Its complete encapsulation is shown. The lower part is a photomicrograph of a tissue section of the tumor at a magnification of 520 times revealing strands of adrenocortical cells including several mitotic figures.

the patient was receiving 2 cc. of adrenal cortex extract (hog) four times daily and 2 cc. of whole aqueous adrenal cortex extract every three hours. The follow-

ing day improvement was maintained, and the doses of adrenal extract were gradually diminished. On the third postoperative day a blood transfusion was given because of anemia.

On the fourth postoperative day the temperature rose to 103 F. and was thought clinically to be due to a widespread pyoderma. Culture of the cutaneous lesions again revealed hemolytic Staph. aureus A. Blood culture was sterile. The organism was fifteen times as resistant as the standard organism to penicillin and more than five hundred times as resistant as the standard organism to streptomycin. It was 50 per cent inhibited by 20 mg. per hundred cubic centimeters of sulfadiazine. Accordingly, dosage of penicillin was increased to 200,000 units intramuscularly every three hours. Wet dressings of tyrothricin solution were applied topically to the skin. The development of pronounced resistance of the organism to streptomycin led to discontinuance of the use of this antibiotic substance. The pyoderma was gradually brought under control; during the fourth postoperative week it again recurred but was promptly controlled on this occasion by the same therapeutic regimen. During this period, an eosinophilia (19 per cent) in the peripheral blood smear was interpreted as probably being due to penicillin sensitivity. Injections of adrenal cortex extract were entirely discontinued during the fourth postoperative week.

Postoperative results of repetition of certain laboratory studies were noteworthy. Roentgenograms of the spine and long bones showed no essential change from the preoperative films. Dextrose tolerance tests at this time showed a flat curve: the level on fasting was 80 mg.; at one-half hour, 100 mg.; at one hour, 85 mg.; at two hours, 85 mg., and at three hours, 75 mg. per hundred cubic centimeters. A twenty-four hour urinary specimen obtained for the determination of 17-ketosteroids two months after operation showed no excretion (total urinary volume, 390 cc.). Blood sodium was 136.4 milliequivalents per liter. Blood pressures varied from 100 to 130 systolic and from 60 to 85 diastolic. During the postoperative period no change in the hirsutism or the size of the clitoris was noted; however, all observers agreed that the obesity, particularly of the face, had lessened despite a slight gain in weight. She was discharged after fourteen weeks of hospitalization, at the age of 15 months.

Follow-Up Report.—The patient was readmitted at the age of 17 months for follow-up study. She had been free of illness in the intervening period. Operation had been performed four months earlier. Her appearance was strikingly altered. Obesity of face, trunk and proximal extremities was no longer apparent. Hirsutism was much less noticeable and there was definite regression of the pubic hair noted during the previous admission. It was the examiner's impression that the labia and clitoris were not enlarged at this time. Her weight was 21¼ pounds (9.9 Kg.) and height 29½ inches (73.8 cm.). Mucous membranes still appeared plethoric despite a mild anemia (hemoglobin concentration was 9.0 Gm. per hundred cubic centimeters; red blood cells numbered 3,650,000, and the hematocrit reading was 38 per cent). The urine was entirely normal with specific gravity of 1.026. Blood electrolytes were within normal limits. Blood pressures ranged from 104 to 120 systolic and from 78 to 80 diastolic. The lower pole of the left kidney was still palpable. There were no cutaneous lesions. Muscle tone had improved. Repeat roentgenograms of skull, spine, long bones, chest and abdomen revealed no essential change from previous films except for operative resection of the right twelfth rib. There was no evidence of metastases. A twenty-four hour urinary specimen was obtained and was demonstrated to contain no 17-ketosteroids.

Subsequent follow-up examinations were obtained at monthly intervals; the last prior to this report was made one year postoperatively. At this examination

the child appeared normal (fig. 4). She had been slow in pulling herself up to a sitting position and in walking but development was essentially normal. The mother stated that the child ate everything given to her but consumed particularly large amounts of protein foods. Her height was 34 inches (85 cm.) and weight was 32 pounds (14.5 Kg.). The blood pressure was 120 systolic and 78 diastolic. There was no evidence of hirsutism or obesity and the external genitalia were normal. The liver was palpable 2 cm. below the right costal margin and the lower pole of the left kidney was again palpable 3 to 4 cm. below the left costal margin. The right ear drum revealed a central perforation and minimal discharge; the left ear drum was normal. However, caloric stimulation of the left canal revealed absence of vestibular response, apparently due to streptomycin

Fig. 4.—Patient eighteen months after operation revealing a normal appearance. Obesity, hirsutism and plethora are no longer apparent and muscular development is much improved.

toxicity. Results of the remainder of the physical examination and the psychometric examination were normal. Examination of a twenty-four hour urinary specimen eighteen months postoperatively again revealed no 17-ketosteroids, indicating absence of metastatic hormone-producing adrenal tissue.

COMMENT

Diagnosis.—The picture of fully developed Cushing's syndrome with minimal virilization, as presented by this patient, is so striking that it may be readily recognized on cursory examination. It is of interest in this connection that the patient reported on by Marks, Thomas

and Warkany (1940), who was the same age as our own, presented a remarkably similar appearance. Other reported cases, however, reveal a considerable range of variation in the degree of admixture of the symptoms of Cushing's syndrome and the virilization usually characterizing the adrenogenital syndrome in both sexes. Our patient did not exhibit striae atrophicae or advanced osteoporosis, features which are usually more remarkable in adult cases. While the "buffalo type" of obesity, confined to face, neck, trunk and proximal extremities, has been most characteristic, a number of cases have been described of children in whom the obesity was more diffuse, involving the abdomen and distal extremities as well (Marks, Thomas and Warkany, 1940).

Differential Diagnosis.—In consideration of differential diagnosis, adiposogenital dystrophy must be differentiated. In this condition there is frequently a family history of obesity, hypogonadism or diabetes. No relevant family history is obtained in cases of Cushing's syndrome. The incidence of adiposogenital dystrophy is equal in both sexes and this condition most frequently occurs in children from 8 to 12 years of age. Cushing's syndrome occurs approximately seven times as frequently in the female as in the male and is rare in this age group. Children with adiposogenital dystrophy exhibit hypogenitalism, delayed puberty and delayed appearance of facial, axillary and pubic hair, while in Cushing's syndrome one sees virilization of the external genitalia and hirsutism. In addition, the other metabolic changes of Cushing's syndrome should help to differentiate these two conditions.

Laurence-Moon-Biedl syndrome may be differentiated by the occurrence of mental retardation, retinitis pigmentosa and abnormalities of bone in the patient and in the family history. Pineal tumors have been reported to cause sexual precocity only in boys; however, moderate obesity has been reported in both sexes. Muscular, osseous and mental precocity have been described. Examination for neurologic abnormalities and roentgenologic studies, including use of air injection methods, may be needed for accurate diagnosis. The other metabolic changes of Cushing's syndrome have not been seen in pineal tumors, with one possible exception (Massobrio and Boccuzzi, 1939), a case cited by Farber and his associates (1946). Tumors of the interpeduncular region at the floor of the third ventricle may cause obesity, sexual precocity and hypertension. The sexual precocity is homologous. Precocious development of the breasts and of the genitalia toward adult type and precocious menstruation are seen in the female. However, since the male patient exhibits virilization, differential diagnosis may be more difficult. Neurologic and roentgenographic findings on utilization of air injection technics, as well as the absence of other signs of Cush-

ing's syndrome, may help to differentiate. Precocious sexuality or puberty in the female child, usually of constitutional type (Novak, 1944), but less frequently due to granulosa cell tumor or other tumor of the ovary or to an interpeduncular tumor as described previously, does not present a serious diagnostic problem, since the precocious sexuality is homologous in type without virilization and there is no associated obesity or other manifestation of Cushing's syndrome. Arrhenoblastoma producing masculinization in the female has not, to my knowledge, been described in a patient under 15 years of age.

Localization of Tumor.—Once the diagnosis of Cushing's syndrome is confirmed, it is necessary to study the patient further in order to localize the site of pathologic change. It is not my purpose here to enter into a detailed discussion of the complex interrelationships among various endocrine glands, particularly those of the pituitary and adrenal glands. This subject, with a discussion of the adrenogenital and Cushing's syndromes, is well described by Soffer (1946). It is noteworthy that this author lists thirteen pathologic abnormalities with which Cushing's syndrome has been associated in the adult. However, diagnosis in the child appears simpler. Marks and others (1940) reported 24 cases of Cushing's syndrome in children before puberty due to benign or malignant tumors of the adrenal cortex. Only 2 of their patients were over 10 years of age. Twenty-seven cases were reviewed by Farber and his associates in 1943. Of these, 4 cases were due to a benign nonmalignant adrenal tumor; 5 cases showed at autopsy a pituitary adenoma; 3 cases were reported as displaying some improvement after pituitary irradiation; autopsy in 3 cases revealed pituitary adenoma and bilateral hyperplastic adrenal glands. One case showed bilateral hyperplastic adrenals, carcinoma of the thymus and a normal pituitary gland; in 2 cases exploratory laparotomy failed to reveal an adrenal tumor, and in 9 other cases the pathologic site could not be established. It is interesting to note, in striking contrast to the cases of tumor of the adrenal cortex reported by Marks and his co-workers, that all the cases reported by Farber and his associates in which pituitary adenoma was present or in which relief was obtained following pituitary irradiation were of persons over 10 years of age. This appears to be a helpful point in localization of the site of pathologic modification. More recently, Gross (1940) reported 2 typical cases of Cushing's syndrome in children which were caused by adrenocortical carcinoma. McQuarrie (1944) added 2 proved cases of Cushing's syndrome due to tumors of the adrenal cortex. In addition, he described a remarkable case, that of a 12 year old girl, in whom the typical picture of Cushing's syndrome developed following a prolonged febrile illness. One year later, with no therapy beyond moderate dietary restriction, all symptoms had disappeared.

It will be interesting to obtain a follow-up report of this case. In this connection, it should be mentioned that cases of Cushing's syndrome have been reported in the absence of gross or microscopic abnormalities in any of the endocrine glands (Guthrie and Emery, 1907). Spontaneous remission may also occur rarely (Cushing, 1932). An exceptional case of Cushing's syndrome due to an encapsulated medullary tumor of the adrenal gland was described recently by Neff and his co-workers (1942).

In recent years a colorimetric method has been developed for the determination of urinary 17-ketosteroids, and values have been determined for normal persons of both sexes at various ages and for various pathologic states. From these data it appears that an excessive excretion of 17-ketosteroids may be expected in the urine in cases of Cushing's syndrome due to pathologic change in the adrenal gland and that normal values will usually be obtained in cases of Cushing's syndrome in which there is no overt adrenal pathologic lesion. The highest titers of 17-ketosteroids are likely to be seen in cases of adrenal tumors, particularly when malignant. Our patient showed a moderate increase in excretion of 17-ketosteroids for her age group. The determination of total urinary 17-ketosteroids helps in the clinical diagnosis and, when excessive in cases of Cushing's syndrome, indicates adrenal tumor or hyperplasia. The determination of beta-ketosteroids before operation may be helpful in distinguishing a malignant adrenocortical tumor from benign hyperplasia or adenoma. Talbot, Butler and MacLachlan (1940) showed a particular increase in the urinary excretion of the beta-ketosteroids in cases of carcinoma of the adrenal cortex.

With the presumptive diagnosis of pathologic change in the adrenal cortex in a case of Cushing's syndrome, the important task remaining is to lateralize the tumor. The value of roentgenographic studies is well illustrated by my own case. I was distinctly surprised to observe the demonstration of a suprarenal tumor on the right by roentgenogram, when on physical examination, a mass, thought to be the lower pole of the left kidney, could be palpated in the left flank. In a problem of this nature, a flat plate of the abdomen, intravenous pyelography with the aid of sectional roentgenography if available and, finally, perirenal insufflation of air should be utilized in an attempt to demonstrate the tumor. Infrequently, calcification within the adrenal tumor may be seen. The use of sectional roentgenography permitted accurate lateralization in the present case (fig. 2).

Treatment.—All cases of Cushing's syndrome in children suspected to be caused by pathologic change in the adrenal cortex should be operated on. Most of these children have tumors, and the majority of

the tumors have proved to be malignant (Marks and others, 1940). Such a decision may be readily made if a suprarenal tumor is lateralized. If no suprarenal tumor can be demonstrated by physical examination and roentgenologic methods, and there is no neurologic or roentgenologic evidence of a pituitary tumor, adrenal exploration is advised if the excretion of urinary 17-ketosteroids is distinctly increased. The likelihood of not finding an adrenal tumor or adrenocortical hyperplasia in a child under 10 years of age with Cushing's syndrome under these conditions is slight. The importance of performing an operation as early as posible is attested to by the high percentage of deaths reported in the literature due to metastases, to intercurrent cerebrovascular or cardiovascular accidents, to intercurrent infections and to inanition. The surgical approach preferred by Cahill and his associates (1936) was transperitoneal via an oblique subcostal incision. Adequate exposure of the tumor is provided and the opposite adrenal gland may be palpated. Young (1937) and Walters and Kepler (1938) favored the posterolumbar approach and, when necessary, performed exposures on both sides at the same operation. The latter approach was used in my patient and permitted rapid and easy removal of the tumor.

The importance of adequate supportive hormonal therapy and of administration of fluid and electrolytes before and after operation cannot be too strongly emphasized. It is my belief that the successful outcome of the present case was made possible by the careful program of supportive therapy outlined by Dr. J. Soffer, of New York, and his co-workers. The purpose of hormone therapy is to support the patient until any remaining atrophic adrenocortical tissue may resume adequate function to support life. Non-hormone-producing adrenal tumors and adrenal tumors associated only with the adrenogenital or virilizing syndrome are not undue operative risks.

Patients with Cushing's syndrome, however, are prone to postoperative acute adrenocortical shock. In 1933, Cecil stated that 39 per cent of patients with Cushing's syndrome operated on died in shock after operation. In 1943, Thompson and Eisenhardt reported that 18 of 22 patients with Cushing's syndrome due to an adrenal tumor died in the immediate postoperative period of shock resembling adrenal insufficiency. In 1947, Spence and Thompson reported on a patient with Cushing's syndrome who died thirty-six hours after the removal of an adrenal tumor. Postmortem examination revealed absence of the contralateral adrenal gland. These authors were able to collect a number of comparable cases from the literature. Cecil (1933) emphasized that in 30 per cent of cases of Cushing's syndrome the adrenal gland on the side opposite the tumor was absent or atrophic. He considered absence of the gland to be advanced atrophy rather than true aplasia.

In 1941, Weinberg reviewed 34 cases of neoplasm of the adrenal cortex in which both glands were examined at autopsy. Twenty-one cases showed atrophy of the contralateral gland. There was complete absence of the contralateral adrenal gland in 2 cases and in 10 cases the contralateral gland was normal. In 1 case there was bilateral adrenal atrophy caused by a tumor in an accessory adrenal gland. It is of interest that Ingle and Kendall (1937) were able to produce atrophy of the adrenal cortex of the rat by administration of large amounts of adrenal cortex extract. Patients with metastases survive the immediate postoperative period because these cells are hormone producing. Patients with Cushing's syndrome due to bilateral adrenal hyperplasia are less prone to postoperative collapse when one entire gland, or a portion of both glands, is removed at operation. The greatest operative risk occurs in those patients with benign adenoma or carcinoma that has not metastasized.

Other suggestions for therapy have been made which seem worthy of clinical trial. Thompson and Eisenhardt (1943) suggested preoperative irradiation of the tumor to diminish its hormonal activity and to stimulate function of the opposite adrenal gland. To my knowledge, this suggestion has not received sufficient clinical trial. Soffer (1946) states that irradiation of the adrenal glands, in cases of adrenocortical tumor or hyperplasia, is ineffective. Further information on the radiosensitivity of these tumors would be desirable.

Most patients with Cushing's syndrome show no electrolyte disturbance (Cahill and others, 1936). A small number of patients has been described who showed elevated blood sodium and bicarbonate and depressed blood potassium and chloride levels (Willson and others, 1940; Soffer, 1946; McQuarrie and others, 1937; Goldzieher, 1939). My own patient showed a moderately elevated blood sodium value. Anderson, Haymaker and Joseph (1938) observed an increased excretion of potassium and a decreased excretion of sodium in the urine of patients with Cushing's syndrome. Desoxycorticosterone has been shown to lower the serum level of potassium and to increase its urinary excretion in normal and in adrenalectomized animals (Thorn and others, 1938). Metabolic studies have indicated that the reduction of blood potassium reflects the depletion of intracellular stores of this electrolyte (Willson and others, 1940). From these data a high potassium, low sodium intake in cases of Cushing's syndrome appears indicated in the preoperative period. Indeed, McQuarrie, Johnson and Ziegler (1937) report subjective improvement, increase in blood potassium and chloride and decrease in bicarbonate toward normal levels in an adult patient with Cushing's syndrome whom they treated with potassium chloride. In the early postoperative period after the removal

of an adrenal tumor, however, a high sodium and low potassium intake should be given, so long as the danger of acute adrenocortical shock persists.

In 1943, Albright presented the hypothesis that one of the principal defects in Cushing's syndrome was an interference with the normal synthesis of tissue protein. This author demonstrated that patients with Cushing's syndrome given methyl testosterone show positive balances for nitrogen, potassium, calcium and phosphorus and a decrease in urinary excretion of 17-ketosteroids. Such patients exhibited thicker skin, stronger muscles, denser bone and a gain in weight, in addition to considerable subjective improvement. A trial of therapy with this hormone may be indicated in cases of Cushing's syndrome, should these findings be substantiated.

Two measures which have induced adrenal hypertrophy in experimental animals (Tepperman and Engel, 1942) are diets high in protein and injections of the adrenotropic factor of the anterior lobe of the pituitary (Collip and others, 1933). High protein diets should be offered to all patients with Cushing's syndrome. In the preoperative period it is doubtful that a positive nitrogen balance will be obtained through dietary measures, except possibly when acompanied by testosterone therapy. The adrenotropic factor of the anterior lobe of the pituitary, if available for clinical use, would be of theoretic value in forestalling the occurrence of acute adrenocortical insufficiency in the postoperative period in cases in which atrophy of the contralateral adrenal gland was not too advanced.

In cases of Cushing's syndrome in which no adrenal tumor or hyperplasia can be demonstrated, irradiation of the pituitary should be performed. Soffer (1946) recommends preoperative irradiation in known cases of pituitary adenoma, since some of these tumors are radiosensitive. However, with the development of increasing neurologic signs and symptoms, surgical intervention is indicated. In the presence of adrenocortical tumor or hyperplasia roentgen treatment of the adrenals or pituitary is ineffective.

Since patients with Cushing's syndrome are particularly susceptible to infections with pyogenic organisms, especially to staphylococcic infections of the skin, the treatment of such infections may be of great importance in the management of the individual case. This problem was convincingly illustrated by the present patient. I feel that the repeated determination of the sensitivity of the offending organism to various chemotherapeutic and antibiotic agents by laboratory methods was a distinct aid in therapy.

Prognosis.—Despite the development of improved diagnostic methods and operative technics and of new hormone preparations, the prognosis of this disease remains poor. All cases of Cushing's disease due

to pathologic changes in the adrenal gland in children who were not operated on resulted in death in six months to four years from the onset of symptoms. A small number of survivors have been reported following operation (Collett, 1924; Walters and others, 1934; Friedgood and Gargill, 1938; Neff and others, 1942). In addition, several cases of remission of Cushing's syndrome in older children have been cited by Farber and his associates (1943), following roentgen irradiation of the pituitary (Cushing, 1932 *b*; Jamin, 1934; Layani and others, 1939). The case reported by Jamin (1934) of a 14 year old boy apparently represented a complete cure following roentgen irradiation of the pituitary. McQuarrie's (1944) case of spontaneous remission is, to my knowledge, the only case of its kind to be reported of a child, and it had an outcome not to be anticipated.

CONCLUSIONS AND SUMMARY

1. A case of Cushing's syndrome in an 11 month old female infant, with onset at 3 months of age, is reported. Apparent surgical cure resulted following the removal of a carcinoma of the right adrenal cortex.

2. Cushing's syndrome is differentiated from the adrenogenital syndrome because of varying symptomatology, clinical course, prognosis and therapy. Differential diagnosis is discussed.

3. Determination of urinary excretion of 17-ketosteroids is shown to be of distinct diagnostic and prognostic value.

4. The importance of special roentgenologic methods for lateralizing adrenal tumors is emphasized. The method of sectional roentgenography (laminagraphy, tomography) proved of value in this case.

5. Early operation in cases of Cushing's syndrome of adrenal origin is recommended to forestall death from tumor metastases, acute cerebrovascular and cardiovascular accidents, intercurrent infections and inanition.

6. The importance of correct medical management in the preoperative and postoperative periods is emphasized.

50 West Ninety-Sixth Street (25).

Members of the endocrine group of the medical service at the Mount Sinai Hospital devised the detailed regimen of hormonal therapy described in this article.

Dr. Murray Bass helped and advised in the preparation of this case report.

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News and Comment

GENERAL NEWS

Short Courses in Diagnosis and Treatment of Poliomyelitis Patients Announced.—The National Foundation for Infantile Paralysis lists the following short courses in the diagnosis and treatment of patients with poliomyelitis for physicians, scheduled during 1949 (as of May 1, 1949):

Training Center	Scheduled Courses	For Detailed Information and Enrollment, Write to:
Children's Hospital, Boston	June 13 to 17; August 15 to 19	William T. Green, M.D.
City Hospital, Cleveland	July 18 to 23; August 8 to 13; August 29 to September 3	John A. Toomey, M.D., Department of Contagious Diseases
D. T. Watson School of Physical Therapy, Leetsdale, Pa.	One to three weeks, depending on individual need; dates to be specially arranged; emphasis on when to prescribe the respirator and when the rocking bed, with variations to meet the needs of each patient	Jessie Wright, M.D., Medical Director
Georgia Warm Springs Foundation, Warm Springs, Ga.	Three to six months, starting July 5 and October 3	Robert L. Bennett, M.D., Director of Physical Medicine
Stanford University School of Medicine, San Francisco	Three days, probably the second week in July	W. H. Northway, M.D., Assistant Dean
University of Colorado Medical Center, Denver	May 23 to 28; November 14 to 19	Winona C. Campbell, M.D,. Director of Poliomyelitis Teaching Program

Sixth International Congress of Pediatrics, Zurich, Switzerland, 1950.—During the Fifth International Congress of Pediatrics in New York, July 14 to 17, 1947, a Committee of Seven (composed of Prof. R. Debré, Paris, France; Dr. F. Gómez Santos, México, D. F. Mexico; Dr. H. F. Helmholz, Rochester, Minn., the former president; Dr. L. Emmett Holt Jr., New York, secretary-general; Dr. Maslow, Leningrad, U. S. S. R.; Dr. A. A. Moncrieff, London, England, and myself, Zurich, Switzerland, who was elected president of the Sixth International Congress of Pediatrics) met in order to draw up rules for the constitution of an International Pediatric Association (I. P. A.).

Pending the acceptance by the International Congress of 1950, this Committee of Seven decided the following:

1. To establish a list of the various national pediatric societies, as well as of their presidents and possibly their members. I, as well as Dr. L. Emmett Holt Jr. (Bellevue Hospital, Twenty-Sixth Street and First Avenue, New York), ask you kindly to send us the required information.

2. To create an *International Reference Journal of Pediatrics.*

3. To give advice to other organizations concerned with child health and welfare.

4. To organize international regional meetings in order to discuss special problems of immediate importance.

Until the coming Congress in 1950, the official communications of the I. P. A. will be published in six languages in the regular numbers of *Helvetica paediatrica acta.* These will be sent free of charge to the presidents of the national societies.

I request that the various national pediatric societies kindly communicate to me, as soon as possible, suggestions for the main subjects to be discussed at the Sixth International Congress of Pediatrics.

G. FANCONI
President, Sixth International
Congress of Pediatrics, 1950.

PERSONAL NEWS

Dr. Stanley Gibson Receives Honorary Degree.—Dr. Stanley Gibson, formerly professor of pediatrics at Northwestern Medical School, received an honorary degree of Doctor of Science from his alma mater, DePauw University, Greencastle, Ind., recently.

NOTICE

Date of Reception of Paper on Vitamin A Absorption.—The authors have requested that mention be made of the fact that the paper "Vitamin A Absorption in the Newborn," by Sobel, Besman and Kramer, published in the May 1949 issue of the AMERICAN JOURNAL OF DISEASES OF CHILDREN, page 576, was submitted for publication Feb. 5, 1948.

Correspondence

BCG VACCINATION

To the Editor.—In the article, "BCG Vaccination in Chicago," by Dr. Robert A. Black in your journal of March, 1949 [p. 381] there appears the following statement, "At present, the Tice Laboratories have been designated as the central laboratories for BCG production for the United States Public Health Service." This letter is occasioned because this statement could easily be misinterpreted.

The Tice Laboratories have been one of the sources of the BCG used by the Public Health Service in research on the vaccine. However, the Public Health Service is also receiving BCG from the Pasteur Institute, Paris, State Serum Institute of Copenhagen, Division of Laboratories and Research of the New York State Department of Health, Albany, and the Pennsylvania Department of Health Laboratory at Henry Phipps Institute, Philadelphia. All of the aforementioned laboratories have been most cooperative and helpful. There is no officially designated central source of the vaccine.

ROBT. J. ANDERSON, Medical Director
Chief, Division of Tuberculosis
Federal Security Agency
Public Health Service
Washington 25, D. C.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Effect of Cooking and Curing on Lysine Content of Pork Luncheon Meat. O. H. M. Wilder and H. R. Kraybill, J. Nutrition **33**:235 (Feb. 10) 1947.

Wilder and Kraybill analyzed pork luncheon meats for lysine and fed them to rats as a supplement to a diet deficient in lysine. Lysine analyses of fresh, cooked and cured-cooked pork luncheon meat indicated that there was no destruction of lysine due to the cooking but that the cured-cooked sample showed a loss of 12 per cent of the original lysine content. No significant differences in growth were observed in rats fed the three samples of meat, indicating that, if there was a destruction of lysine, it was too small to detect in the feeding tests with rats.

Fredeen, Kansas City, Mo.

Work Performance, Respiratory Exchange, and Certain Blood Constituents After Isocaloric Meals of Low and High Carbohydrate Content. John Haldi and Winfrey Wynn, J. Nutrition **33**:287 (March) 1947.

In the treatment of the clinical syndrome of functional hypoglycemia, a reduction in the carbohydrate intake has been observed in a number of instances to give good results. It is probably on the basis of such observations that some workers have been led to believe that relatively high carbohydrate meals predispose normal persons to hypoglycemia, with a concomitant feeling of weakness and a diminution in the capacity for work. The present experiments done by Haldi and Wynn on normal healthy adolescents and adults do not support this point of view. Several hours after the ingestion of a high carbohydrate meal, there was no evidence of hypoglycemia either before or immediately after severe, exhausting exercise. Work output, percentage recovery and muscular efficiency were not diminished by the relatively large carbohydrate intake. These observations afford confirmatory evidence as drawn from previous studies that the hypoglycemic syndrome of functional origin is a pathologic condition and not a normal psysiologic response to an antecedent high carbohydrate intake.

Fredeen, Kansas City, Mo.

Improving the Nutritive Value of Flour: I. The Effect of Supplementing Enriched Flour with Other B-Complex Vitamins. Beulah D. Westerman and Gertrude Hall, J. Nutrition **33**:301 (March) 1947.

Westerman and Hall conducted experiments to show that the supplementation of enriched flour with certain vitamins of the B complex improves the nutritive value of the flour. Flour enriched at the levels recommended by the National Research Council with thiamine, riboflavin and nicotinic acid, when used as the sole source of the B complex vitamins does not supply enough of these vitamins to support normal growth in rats when fed at a level of 40 or 50 per cent of the diet. While flour and bread are not necessarily expected to supply all the B complex vitamins in the diet, it might be well to have more of these vitamins supplied by the cereal foods, inasmuch as cereals make up a major portion of the food intake of so many people in the world. Under the conditions of their experiments, the addition of 1 microgram of riboflavin per gram of enriched flour produced an

increase in the growth rate of the animals. Even greater growth of the rats was stimulated by the addition of 1 microgram each of riboflavin and thiamine to the enriched flour. A still greater increase in growth resulted when 20.5 micrograms of calcium pantothenate and 7 micrograms of pyridoxine per gram were added to the enriched flour.

FREDEEN, Kansas City, Mo.

A STUDY OF THE RELATION BETWEEN PROTEIN EFFICIENCY AND GAIN IN WEIGHT ON DIETS OF CONSTANT PROTEIN CONTENT. D. M. HEGSTED and JANE WORCESTER, J. Nutrition **33**:685 (June) 1947.

Hegsted and Worcester investigated, by feeding experiments with young rats, the nutritive value of 23 different proteins or protein mixtures. All diets contained 12 per cent protein. There was a high correlation between gain in weight and protein efficiency (gain per gram of protein eaten). Protein efficiency was a function of gain in weight rather than a characteristic of the type of protein fed. In studies on the relative nutritive value of various proteins with the use of growing rats fed *ad libitum*, little additional information was gained by taking into account the amount of protein eaten, i.e., the calculation of protein efficiency.

FREDEEN, Kansas City, Mo.

COMPARATIVE NUTRITIVE VALUE OF CASEIN AND LACTALBUMIN FOR MAN. ARTHUR J. MUELLER and WARREN M. COX JR., J. Nutrition **34**:285 (Sept.) 1947.

Mueller and Cox fed casein and lactalbumin at an intake level of 2 per cent of the calories to 4 well adults, following a twelve day protein depletion diet. Two four day periods of supplementation with each protein were alternated with four day depletion periods. The results of the present experiment, in which the two proteins have been compared at low intake levels in healthy but slightly protein-depleted adults, showed that casein and lactalbumin were of equal value for adult maintenance.

FREDEEN, Kansas City, Mo.

CALCIUM ENRICHED MEAT COMPARED WITH MILK AS SOURCE OF CALCIUM PHOSPHORUS AND PROTEIN. IRVINE MCQUARRIE, MILDRED ZIEGLER and IRWIN H. MOORE, Proc. Soc. Exper. Biol. & Med. **65**:120 (May) 1947.

Calcium, phosphorus and protein balances were calculated for 2 boys 12 and 14 years of age, who were maintained for fifteen days on a milk-containing diet. The results were compared with those obtained in a twelve day period while the subjects were on a diet of calcium-enriched ground beef which was comparable as regards the aforementioned nutrients. These diets appeared to be equally good as sources of calcium, phosphorus and protein. Similar results were observed in young rats placed on the same type of diets as judged by weights of femurs and analyses of carcass ash.

HANSEN, Galveston, Texas.

BREAST FEEDING FROM THE OBSTETRICAL POINT OF VIEW. HOWARD C. WALSER, in Senn, M. J. E.: *Problems of Early Infancy*, Transactions of the First Conference, March 3-4, 1947.

The interested obstetrician can help increase the number of nursing mothers by proper approach to the subject, beginning early in pregnancy. By casual remarks and by apparently assuming that the mother will nurse the baby, the idea can be implanted in the mother's mind without the need of arguments or lectures.

MCGUIGAN, Evanston, Ill.

Vitamins; Avitaminoses

EFFECT OF NICOTINIC ACID ON THE BLOOD LIPIDS OF NORMAL INFANTS. O. IMPERATO and U. CORUZZI, Lattante **18**:135 (March) 1947.

Daily injections of 20 mg. of nicotinamide were given to 6 infants, 5 to 16 months old. After the third injection, the blood lipid level before breakfast had increased from 6 to 14 per cent. The infants showed a gain in weight with the rise in blood lipid content.

HIGGINS, Boston.

PHOSPHATEMIA AND THE CLINICAL SIGNS OF RICKETS: THEIR RELATION TO MASSIVE DOSES OF VITAMIN D. M. SAGGESE, A. DE LUCA and V. BAFFI, Pediatria **55**:20 (Jan.-March) 1947.

From researches on 45 rachitic children made in collaboration with the Italian Medical Nutrition Mission, United Nations Relief and Rehabilitation Administration, the authors noticed a relation between the increase of alkaline phosphatase in the blood serum, as determined by the King-Armstrong method, and the evolution of the rachitic process.

They gave a single dose of 20,000 to 50,000 international units of vitamin D_2, with control of blood phosphatase activity. On clinical examination a month later, they came to the conclusion that such treatment is good only for the light cases of rickets and useless for the severe ones.

FROM THE AUTHORS' ABSTRACT.

SUBPERIOSTEAL HEMATOMA IN RICKETS (MOELLER-BARLOW DISEASE). JOSEPH HOUSTEK, Pediat. listy **1**:75, 1946.

This disease is rare in Czechoslovakia. A case of an 8 month old infant is described, with typical clinical and roentgenographic findings. Of interest are the atypical vitamin C levels in the blood. The roentgenographic diagnosis in the early stages of this disease is discussed in detail.

FROM THE AUTHOR'S SUMMARY.

Hygiene; Growth and Nutrition; Public Health

A NEW STATE PROGRAM OF SPEECH REEDUCATION IN VIRGINIA. JAMES M. MULLENDORE, Quart. J. Speech **33**:361 (Oct.) 1947.

The University of Virginia reestablished a speech clinic in 1945 for the coordination of a statewide program, as the result of campaigning by the University Hospital, members of the State Department of Education and the Virginia Society for Crippled Children and school administrators and supervisors. It was, therefore, felt that the clinic should serve, as far as possible, in the development of the training program and, in general, provide a long range clinic program. Questionnaires were sent to every division superintendent in the state. Approximately 70 per cent responded. A number of counties were surveyed, screening children into categories of satisfactory speech, slightly defective speech, moderately defective speech and severely defective speech. The state of Virginia will support part of the salary of speech correction specialists, but it has been difficult to find such persons to take part in the state program. The author states that concerted effort by every interested, professional worker in any state is necessary to develop a real program on a statewide basis.

PALMER, Wichita, Kan.

OUR HIGH INFANTILE MORTALITY RATES. H. NELSON, South African M. J. **21**:695 (Sept. 27) 1947.

Nelson surveyed the infant mortality rate in Pretoria, South Africa, taking in all economic and racial groups. He observed that there has been a substantial decrease in mortality, that this reduction is most pronounced in the upper economic groups, that the mortality rate increases as the economic position deteriorates and that most of the causes of infant deaths are preventable. He expresses his feeling that the rate cannot be reduced extensively unless all human beings have the essential amenities of life and he recommends a remodeling of the economic system so that all shall earn sufficient wages to purchase the necessities.

McGUIGAN, Evanston, Ill.

INFANT AND CHILDHOOD MORBIDITY IN SALZBURG FOLLOWING THE WAR. GOTTFRIED ZEDERBAUER, Wien. klin. Wchnschr. **58**:598 (Oct. 11) 1946.

From his observations up to April 1946, Zederbauer noted no increase in the childhood morbidity rates for malnutrition, avitaminoses or infectious diseases. Case incidence of scabies has shown a pronounced rise during 1945-1946.

However, the author noted a decided increase in infant mortality and morbidity since 1938, particularly in infantile diarrhea. He noted that early weaning of the infant, as practiced in Austria, is probably the cause of the increased morbidity and mortality from these diseases. Besides the increased rate of incidence for the diarrheal diseases, the author noted an increased incidence of pyoderma in young infants, as well as in increased number of premature births, with a mortality of more than 50 per cent. The author warned that the practice of early weaning of infants threatens the future of the Austrian people.

ABT, Chicago.

Prematurity and Congenital Deformities

CONGENITAL GIANT THUMB. EMANUEL B. KAPLAN, Bull. Hosp. Joint Dis. **8**:38 (April) 1947.

A normal 24 year old white man had a large right thumb since birth. In the past two years it had become larger and there was tingling in the third and fourth fingers. Two plastic operations were performed sixteen months apart. The flexor tendons, median nerve, vessels and ulnar nerve were matted together in a fibrous mass, and large amounts of enveloping fibrolipomatous tissue were removed. The pathologic diagnosis was localized neurofibromatosis of thumb and thenar eminence. After the first operation, the thumb became smaller but with some restriction of motion. In the second operation, yellowish fibrous tissue entwined the median nerve at the wrist to such an extent that it could not be removed. The functional and cosmetic result was good, but some swelling of the wrist and slight numbness in the middle finger still persisted after nearly two years.

KIMBALL, Evanston, Ill.

THE EFFECT OF PREGNANCY COMPLICATED BY ALLOXAN DIABETES ON THE FETUSES OF DOGS, RABBITS AND RATS. HERBERT C. MILLER, Endocrinology **40**:251 (April) 1947.

The experiments described were undertaken on dogs, rats and rabbits to determine whether or not it was possible to reproduce in animals some of the many striking phenomena that have been observed in the human fetus of the diabetic mother. It is well established that fetal and neonatal mortality is increased

among infants born to diabetic mothers and that there is a strong tendency for the human fetus to have an increased weight at birth without evidence of a prolonged gestation period. Changes in the viscera and endocrine glands of some infants born to diabetic mothers have also been reported. Among these changes have been described cardiac enlargement, increased glycogen content of the myocardium and increased erythropoiesis in the liver and other tissues, increased eosinophilia in the anterior lobe of the hypophysis, hyperplasia of the adrenal glands, hyperplasia of islands of Langerhans and hyperplasia of the gonads.

Since the high mortality rate and the strong tendency toward an increased weight at birth are the two outstanding characteristics among infants born to diabetic mothers, information on these two qualities was primarily sought in the animal experiments here reported.

It was observed that diabetic pregnancies in rabbits resulted in many abortions, premature deliveries, stillbirths and the deliveries of immature fetuses. About half of the diabetic pregnancies were full term. No evidence of an increased weight at birth among the fetuses of diabetic rabbits was seen. All the pregnancies of diabetic rats were full term and resulted in the birth of healthy fetuses that had normal weights at birth.

JACOBSEN, Buffalo.

RELATIONSHIP BETWEEN MATERNAL ANCESTRY AND INCIDENCE OF CLEFT PALATE. HENRIETTA C. KRANTZ and FLORENCE M. HENDERSON, J. Speech Disorders **12**:267 (Sept.) 1947.

Ninety-three cleft palates were found among 47,153 recorded live births between Jan. 1, 1942 and Jan. 1, 1947. The study of the ancestry in these births leads to the following conclusions. 1. The comparatively high rate of cleft palates in Hawaii is due to the racial composition of the population of the islands. 2. The tendency toward the production of the cleft palate in children is positively correlated with the number and recency of fusion of racial fractions in maternal ancestry. 3. Whatever the actual causation of cleft palate, it seems to be carried, in some instances at least, as a transmissible genetic factor whose phenotypic expression is augmented as a result of racial blending in the maternal ancestry.

PALMER, Wichita, Kan.

A VELOPHARYNGEAL EXERCISE. FRANCES M. BROWN, J. Speech Disorders **12**:279 (Sept.) 1947.

A loose cap is constructed from a small piece of paper to fit over the nares. The parents and the child with cleft palate play with the caps on in order to develop conscious control of blowing through the mouth.

PALMER, Wichita, Kan.

Newborn

ANOXIA NEONATORUM. CHARLES LEAVITT SULLIVAN, New England J. Med. **235**:894 (Dec. 19) 1946.

It is vital for one to remember that the newborn baby who does not breathe normally is either in or close to a condition of shock and that the utmost gentleness, along with the conservation of body heat, is mandatory. The airways must be cleared immediately and completely. It is best to start treatment with the administration of pure oxygen to combat anoxia and shock and, when this purpose is accomplished, if a satisfactory respiratory response has not been made, to shift to the administration of 5 per cent carbon dioxide in an attempt to stimulate the

respiratory center. All infants requiring treatment for anoxia should be given the same meticulous care and attention accorded premature infants and should be placed in an incubator at a temperature of approximately 90 F. with continuous administration of oxygen for from six to twelve hours, the babies being at all times under careful observation.

GENGENBACH, Denver.

THE LEUKOCYTIC FORMULA IN THE NEWBORN IN RELATION TO THAT IN THE MOTHER AND THE ENDOCRINOLOGY OF GESTATION. ANGELO INGUILIA and GIORGIO DE GIOSUÈ, Riv. clin. pediat. **45**:129 (March) 1947.

After making simultaneous studies of the blood formula in the mother and in the newborn, the authors observe that modifications noticeable in the white blood cells (on which they have focused their attention) happen in a synchronous and parallel manner in the two organisms. Also, the evidence in the literature that the modifications of the leukocytic formula in the mother and in the fetus are also determined in a synchronous and parallel manner during gestation and correspond to the variations in the various tendencies of the maternal sex hormones has induced the authors to assign the variations which they observed to hormone factor.

Large doses of follicular hormone given to a group of newborn infants in the first week of life have resulted, in some of them, in a delay in the appearance of inversion of the leukocyte formula and, in others, in the persistence of neutrophilic leukocytosis. These results seem to confirm the authors' hypothesis.

FROM THE AUTHORS' SUMMARY.

PAROXYSMAL TACHYCARDIA IN THE SMALL INFANT. P. L. LUQUE and A. S. SEGURA, Arch. argent. de pediat. **26**:350 (Nov.) 1946.

A brief review of the literature concerning paroxysmal tachycardia in the small infant is given. Continuous crying, pallor, cyanosis, vomiting and anorexia are pointed out as practically constant symptoms. These symptoms are followed by symptoms of heart failure if the attack persists.

The best treatment in these cases is administration of digitalis, and this drug was used in both cases reported. The first case was that of a 1 month old child with an attack of auricular paroxysmal tachycardia and severe heart failure; the attack ceased when digitalis was given. Twenty months after the attack, the observation of an enlarged heart suggested a congenital heart disease as a primary cause. The second case reported was similar clinically, but in it an interventricular septum defect was evidenced by angiocardiography.

ROJAS, Boston.

Acute Contagious Diseases

THE DICK TEST IN MILITARY PERSONNEL. LOWELL A. RANTZ, PAUL J. BOISVERT and WESLEY W. SPINK, New England J. Med. **235**:39 (July 11) 1946.

The reaction to Dick toxin of 1,280 white men of military age was studied. The frequency of positive reactions was least in men over the age of 20 and in those who had had more than twelve months of military service.

Positive Dick reactions were infrequent in men whose residence before they went into military service had been in a geographic area in which the incidence of hemolytic streptococcus disease is known to be low.

It is concluded that exposure to the hemolytic streptococcus is essential for the establishment of a positive Dick reaction.

The Dick reaction is probably the result of acquired hypersensitivity to the products of the streptococcus rather than of a natural susceptibility to a true toxin.

FROM THE AUTHORS' SUMMARY.

MEDICAL PROGRESS: ACTIVE IMMUNIZATION. GEOFFREY EDSALL, New England J. Med. **235**:328 (Sept. 5) 1946.

Spectacular as have been the advances in recent years in research on influenza, it cannot be said that, if faced with a disaster such as that of 1918, the medical profession is yet in a position to do anything very dramatic in order to prevent its spread. The virus responsible for the next pandemic will almost certainly be one that is unrelated to those now isolated. For this reason it will be necessary first for the virus to be isolated. Vaccines compounded from presently known strains will almost certainly be useless.

Reference is made to Ratner's statement that the ideal age for vaccination for smallpox is between three and six months and to his citation of data regarding neonatal vaccination, which principally confirm the general impression that successful reactions at this age are undependable. It is almost universally agreed that vaccination should be performed not later than the first year of life.

Rabies vaccine is usually administered in case of (*a*) a definite bite by an animal proved rabid, (*b*) a definite bite by an animal in which the possibility of the existence of rabies cannot be excluded—either the animal has been lost track of or pathologic examination has been inconclusive—or (*c*) any definite bite on the head or neck (treatment should be given while the animal is being observed and should be suspended if the animal is well seven days after the bite).

GENGENBACH, Denver.

SCARLET FEVER. A. DANIEL RUBENSTEIN and GEORGE E. FOLEY, New England J. Med. **235**:533 (Oct. 10) 1946.

Between Jan. 2 and May 24, 1945, a total of 94 cases of scarlet fever occurred in a community with a population of 6,611, as compared with 15 cases reported in 1943 and 1 case in 1944. The hemolytic streptococci isolated from 71 (76 per cent) of these cases were classified according to serologic type. Seven types were encountered: types 2, 1, 19, 6, 10, 8 and 9, in order of frequency. The type pattern was similar to that previously observed in other Massachusetts communities during the period when the community considered in the article was experiencing little scarlet fever.

Seventy-one cases (76 per cent) occurred in children of school and preschool age. The first case appeared in grade 3 of school 1 and was followed by a sharp outbreak of 11 additional cases in that room. Types 2, 1 and 19 appeared almost simultaneously in this schoolroom. Cases in other rooms of the same school were followed by the appearance of the disease in other schools in the community.

In the entire outbreak 49 families were involved. Of these, 14 contributed 53, or 64 per cent, of all the cases occurring in the community. In each case multiple infections in the same household were due to the same serologic type. Familial contact accounted for the appearance of sporadic cases in various schools other than those in which the primary cases originated.

FROM THE AUTHORS' SUMMARY.

Acute Infectious Diseases

COMPARATIVE EFFECT OF PENICILLIN AND SULFONAMIDE DRUGS ON THE IMMUNE RESPONSE OF RABBITS TO PNEUMOCOCCUS INFECTION AND THE RELATION OF IMMUNITY TO BACTERIAL CHEMOTHERAPY. PRESTON E. HARRISON, J. Infect. Dis. **79**:101 (Sept.-Oct.) 1946.

When treatment with it is started soon after infection, penicillin, in conjunction with natural immunity, is able to eliminate the infection before antibody response is induced. On the other hand, incomplete bacteriostasis and the lag in activity of sulfonamide drugs allow multiplication of pneumococci, so that a suitable amount of antigen is formed after the initiation of therapy; subsequently, because the drug is started early, the infection is held in check and an optimum antigen-antibody balance is maintained. Under these conditions sulfonamide-induced bacteriostasis is followed by a high titer antibody response. When initiation of therapy is delayed, penicillin appears to be able quickly to control the infection, so that excess antigen in the form of cells and soluble substance is not formed and a high titer antibody response is obtained. The less therapeutically active sulfonamide drugs appear to allow the infection to persist, as is evidenced by positive blood cultures, with corresponding formation of fresh antigen, which uses up formed antibody and results in reduced titer of the circulating antibody.

While successful penicillin therapy appears to be relatively independent of an immune mechanism, the participation of some type of immunity cannot be excluded; it appears, however, that the immune mechanism is much less important to penicillin therapy than to sulfonamide therapy.

TOOMEY, Cleveland, Ohio.

THE USE OF SULFADIAZINE AND PENICILLIN FOR TREATMENT OF EXPERIMENTAL ANTHRAX. F. M. SCHAIBLE JR., H. R. REAMES AND R. D. HOUSEWRIGHT, J. Infect. Dis. **79**:140 (Sept.-Oct.) 1946.

The experiments described demonstrated that monkeys can be infected with Bacillus anthracis if one places the organisms on abraded skin. Sulfadiazine in blood levels of 5.0 to 10.0 mg. per hundred cubic centimeters prevented infection and/or death, with a mortality rate of 7 per cent for treated monkeys compared with one of 85 per cent for untreated animals. Survivors could not be reinfected.

Six monkeys with bacteremia following infection by the cutaneous route survived after treatment with penicillin.

Treatment with penicillin started one hour after infection of mice by the subcutaneous injection of B. anthracis protected 90 to 100 per cent of the animals. Delay in treatment reduced the effectiveness of the drug; therapy beginning forty-eight hours after inoculation seldom protected more than 5 to 10 per cent of the mice. Similar results were obtained when rabbits were used as the experimental animal.

TOOMEY, Cleveland.

A LABORATORY INFECTION WITH PSITTACOSIS VIRUS TREATED WITH PENICILLIN AND SULFADIAZINE, AND EXPERIMENTAL DATA BEARING ON THE MODE OF INFECTION. THEODOR ROSEBURY, HAROLD V. ELLINGSON and GORDON MEIKLEJOHN, J. Infect. Dis. **80**:64 (Jan.-Feb.) 1947.

In a case of acute pneumonitis in a laboratory worker, a tentative diagnosis of psittacosis was made on the basis of symptoms and a history of exposure to

the virus. Intensive penicillin therapy was begun on the fourth day of illness, and, because of a possibility of exposure to Malleomyces pseudomallei, sufadiazine therapy was begun in addition on the following day. Remission of fever and symptoms occurred within thirty-six hours after initiation of penicillin therapy. Psittacosis virus, similar in properties to the strain implicated in the history of exposure, was subsequently isolated from sputum taken on the third day of illness; and a complement-fixing titer of 1:160 against the psittacosis group of viruses was obtained in a specimen of serum taken on the twelfth day, specimens taken earlier having had appreciably lower titers. Tests for infection by other agents were negative. The diagnosis of psittacosis was thus amply confirmed. The dramatic recovery that followed institution of chemotherapy is in line with animal experiments which show that this strain of psittacosis virus is sensitive to both penicillin and sulfadiazine.

The history of exposure involved an ampule of frozen concentrated virus which was found to have a minute perforation at its base. Twelve days before the onset of symptoms the patient, having handled the ampule as its contents were beginning to thaw, had noted a fine jet issuing from its base and impinging against the palm of his hand. Subsequent simulation of this incident, using the same ampule containing a suspension of Serratia marcescens, indicated the production of a viable aerosol with a concentration at the level of the patient's upper respiratory passages which seemed sufficient to account for the infection. The concentration of the aerosol thus experimentally produced was found to be considerably greater in still than in circulating air.

The findings are believed to throw light on the general problem of air-borne laboratory infections due to highly infective agents and to suggest means for their prevention.

TOOMEY, Cleveland.

TYPHOID FEVER IN VACCINATED LABORATORY WORKERS. THOMAS A. HAEDICKE, J. Infect. Dis. **80**:113 (Jan.-Feb.) 1947.

Four previously vaccinated laboratory workers, while working with material containing typhoid bacilli, had typhoid with an atypical clinical picture. The diagnosis was difficult in all cases because of the absence of the usual signs and symptoms. The clinical course in all 4 patients was less severe than that usually seen in patients who have not been vaccinated. There was little similarity between the temperature curves. All patients were only mildly ill. The average length of time during which the temperature was elevated was five and one-half weeks. There were no complications in this series. A review of the literature in which similar cases were reported showed essentially the same type of course in all patients.

TOOMEY, Cleveland.

FURTHER EVALUATION OF THE SKIN TEST FOR FILARIASIS IN MAN, BASED ON RESULTS OBTAINED IN BRITISH GUIANA. D. R. A. WHARTON, J. Infect. Dis. **80**:117 (Jan.-Feb.) 1947.

Two hundred and fifteen persons at the public hospital and the almshouse at Georgetown, British Guiana, were tested with an antigen of Dirofilaria immitis in a dilution of 1:100,000, controlled by a corresponding dilution of dog serum. Of the group, 89.8 per cent reacted positively, 5.1 per cent had negative reactions, and 5.1 per cent gave indeterminate reactions.

No difference in response could be detected among the various racial groups, especially between the Negroes and East Indians, nor could any difference be seen in the younger and the older age groups.

Twenty-two out of 23 children between 3 and 10 years of age reacted positively, this observation indicating a general early infection of the population.

Reactions for 26 out of 29 persons with old elephantoid forms of the disease were positive; for 1, negative, and for 2, indeterminate because of hypersensitiveness to dog serum.

The expression "indeterminate" is proposed for those reactions in which, both reagents being reactive, the response to the filarial antigen is less than 3 mm. greater than that to the dog antigen. This is a correct designation, since the inclusion of dog serum in the control injection does away with the anomaly of the false positive reaction in most cases and greatly improves the significance of the test.

The antigen has been shown to be even more effective than was previously estimated, and it is again recommended for its dependability, safety, ease of application and time-saving character.

TOOMEY, Cleveland.

Diseases of Blood, Heart and Blood Vessels and Spleen

THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN IN PEANUT OIL AND BEESWAX. ARTHUR J. GEIGER and JESSAMINE R. GOERNER, New England J. Med. **235**:285 (Aug. 29) 1946.

Apparent cure in 2 cases of subacute bacterial endocarditis due to Streptococcus viridans was effected with one or two daily injections of massive doses of penicillin in oil and wax U. S. P.

In another case, which had proved refractory to cure after ten months' treatment with water-soluble penicillin given parenterally, an afebrile and asymptomatic state with sterility of the blood was maintained with a single daily injection of penicillin in oil and wax. Positive cultures of the blood, however, were obtained whenever this treatment was discontinued. It is believed that the disease can be kept indefinitely in a state of remission in this patient by this simple ambulatory form of treatment.

Satsifactory concentrations of penicillin in the serum were present for twelve hours and often for twenty-four hours after a single injection of from 300,000 to 600,000 units of penicillin in oil and wax.

FROM THE AUTHORS' SUMMARY.

CHRONIC HYPOPLASTIC ANEMIA. JAROSLAV LHOTÀK, Pediat. listy **2**:160, 1947.

Three cases of children with hypoplastic anemia in the peripheral blood flow are described. In 1, the disease was the result of chronic malnutrition; in another, a congenital anemia of the Benjamin type, and, in the third, a splenic panhematopenia. The clinical picture of hypoplastic anemia and treatment of the disease, especially the indications for splenectomy, are discussed.

FROM THE AUTHOR'S SUMMARY.

ESTIMATION OF THE VELOCITY OF BLOOD FLOW IN CHILDREN BY MEANS OF FLUORESCEIN. ZDENKA HLOUSKOVÁ and JOSEF HOUSTEK, Pediat. listy **2**:167 1947.

The fluorescein method was used for the estimation of the velocity of blood flow in 113 children. In 63 children without any defect in the circulation the

following results were obtained: 7.5 to 10 seconds in children up to 2 years; 10 to 12.5, up to 6; 12.5 to 15, up to 14, and 15 to 17.5, over 14. Values with the micromethod (the estimation of fluorescein in capillary blood) were 2.5 seconds lower for figures over 10 seconds. In anemia a decided increase in velocity was found. In a group of 24 patients with heart diseases there was a pronounced retardation of rate in cases of beginning or obvious decompensation. Values in some other diseases are given. After instruction of the personnel, the method is suitable for older children, especially when samples of blood are withdrawn at 2½ second intervals. It reveals useful information about the state of the circulatory system.

FROM THE AUTHORS' SUMMARY.

CONGENITAL HEART BLOCK. LADISLAV SABATA, Pediat. listy **2**:179, 1947.

Two cases of congenital heart defect with a sinoauricular block, in a newborn and in an infant of 4½ months, are described.

FROM THE AUTHOR'S SUMMARY.

Nervous Diseases

COMPLICATIONS OF INTRATHECAL USE OF PENICILLIN. THEODORE C. ERICKSON, MABEL G. MASTEN and HENRY M. SUCKLE, J. A. M. A. **132**:561 (Nov. 9) 1946.

In 4 cases complications occurred following intrathecal administration of penicillin. In 3 of these the penicillin had been injected intraspinally. From these cases and those previously reported, it appears that the most frequent and characteristic reaction occurs in the meninges, leading to adhesive spinal arachnitis and in the severer cases to transverse myelopathy. In 1 case recovery from such a lesion of the spinal cord followed decompressive laminectomy and aspiration of an intramedullary cyst. In another case, signs of damage to the brain stem occurred following the injection of penicillin into the cavity of a cerebellar abscess, from which the penicillin leaked into the basal cisternae.

The important factors in the production of toxic complications are (1) the concentration of the penicillin solution, (2) the slow diffusion of the spinal fluid, (3) the size of individual doses, (4) the frequency of infection and (5) the duration of intraspinal therapy.

The occurrence of these complications may be minimized by using a dilute solution of penicillin, by avoiding the use of a large total dosage and by limiting the number of injections to the minimum. Further, in consideration of the altered hematoencephalic barrier in disease, it is suggested that greater reliance be placed on early treatment with maximum doses of parenterally injected penicillin and that, when possible, intraspinal administration be avoided.

FROM THE AUTHORS' SUMMARY.

MENINGORADICULITIS AND THE SYNDROME OF GUILLAIN-BARRÉ AND STROHL. A. LAMENZA and S. SANTYAN Y VELASCO, Riv. di clin. pediat. **44**:585 (Oct.) 1946.

From observations on 4 cases of acute meningoradiculitis in children, this illness is discussed, especially in relation to the syndrome of Guillain-Barré and Strohl. The various data, the symptoms and the clinical course of the cases examined are analyzed, from which analysis the particular nosologic entity of

the clinical syndrome, as described by the Belgian authors, appears doubtful. These personal observations, and especially those in 1 case, offer the opportunity for a clinical discussion of its relation with poliomyelitis (Heine-Medin disease), which may often show meningoradicular symptoms. Therefore, the possibility that some meningoradiculitis may be associated with a nonaxial localization of poliomyelitis virus cannot be excluded. FROM THE AUTHOR'S SUMMARY.

PNEUMOCOCCIC MENINGITIS SUCCESSFULLY TREATED WITH SULFONAMIDE COMPOUNDS AND PENICILLIN. J. M. MACERA and E. F. CRISCUOLO, Arch. argent. de pediat. **26**:257 (Oct.) 1946.

This is merely a report of a case. The clinical history is included.

ROJAS, Boston.

Diseases of the Genitourinary Tract

ENURESIS AND SLEEP. R. LACASSIE, Presse méd. **54**:119 (Feb. 23) 1946.

In most persons with enuresis, sleep is much deeper than normal. At the same time an elective mechanism is present which causes the sleeper to ignore some external stimuli and to wake at others. Dreams enter into the problem of enuresis, particularly in adults. The dream of urination should be the signal for arising, but in enuretic persons it is ignored. The author uses amphetamine sulfate to keep sleep from becoming too deep and reports that enuretic patients respond to the need for urination by waking.

DAFFINEE, Melrose, Mass.

ACUTE ADRENAL INSUFFICIENCY IN INFANCY. M. DEL CARRIL, A. LARGUÍA and J. D. VIDAL, Arch. argent. de pediat. **25**:391 (June) 1946.

The authors divide their discussion into three sections: (1) diagnosis and classification of the adrenal insufficiencies; (2) acute adrenal insufficiency in infectious diseases, and (3) adrenal cortex insufficiency in nutritional disturbances.

1. The authors consider as important the following signs and symptoms of acute adrenal insufficiency: sudden onset; hyperthermia and hyperpyrexia; purpuric patches on the skin and mucosas; peripheral circulatory insufficiency, and local and associated symptoms, among which they include gastrointestinal symptoms (anorexia, diarrhea, vomiting), symptoms referable to the central nervous system (convulsions, coma, muscular contractions) and pulmonary congestive phenomena. The following laboratory findings are considered of help in diagnosis: concentration of plasma electrolytes, hypoglycemia, increase of sensitivity to insulin, reduction of adrenal hyperglycemia, decrease of urinary excretion of 17-ketosteroids, increase in the urinary elimination of sodium and chlorides and retention of potassium. Therapeutic tests are also of aid in the diagnosis.

2. The infectious conditions in which the syndrome of acute adrenal insufficiency is present are diphtheria, some epidemics of grip, pneumonia and scarlet fever. Adrenal insufficiency has also been described in cases of malaria, dysentery and typhoid. In all these infections the patient loses ground, and peripheral circulatory insufficiency appears, with which adynamia, diarrhea and vomiting may be associated.

The authors advise as treatment the early and sufficient administration of cortical extracts, an abundant supply of sodium chloride and dextrose and high doses of ascorbic acid. The therapeutic action of epinephrine is discussed.

3. Adrenal cortex failure associated with acute nutritional disturbances is the subject of this section. Humoral, therapeutic and pathologic tests are considered. The authors conclude: 1. The similarity of acute nutritional disturbances and the humoral picture of acute adrenal insufficiency is only apparent. 2. The physiopathologic conditions leading to hyponatremia and hypochloremia, as well as the results of the hyperkaliemia and hypoglycemia, are worthy arguments against acute cortical failure as a primary pathogenic factor in acute nutritional disturbances.

The clinical and laboratory observations on a number of infants (22, or more, records from the cases of others and 6 case studies by the authors) with acute adrenal insufficiency, from the service for lactating infants, Children's Hospital in Buenos Aires, are given in detail.

From the therapeutic point of view, the addition of total cortical extracts to treatment does not modify the evolution of the disease. Effective results are expected only in cases of secondary adrenal insufficiency. Autopsy revealed no lesions except in cases of secondary damage to the adrenal cortex.

ROJAS, Boston.

ACUTE NEPHRITIS IN CHILDHOOD. JOSEF HOUSTEK, Pediat. listy **1**:25, 1946.

A series of 134 cases of acute nephritis is analyzed, of which 35 developed after impetigo. Cases of nephritis following scarlet fever were excluded. Sulfonamide drugs were used in 67 cases. This method of treatment is stressed particularly in acute focal nephritis and in cases with a large number of leukocytes in the urine. Cases of nephritis after impetigo were followed with great care and the course of illness and the laboratory findings are compared with those in cases of other types of nephritis.

FROM THE AUTHOR'S SUMMARY.

BLOOD TRANSFUSIONS IN NEPHRITIS. JAROSLAVA MICHALICKOVA, Pediat. listy **1**:69, 1946.

To 51 patients with acute hemorrhagic nephritis, a small transfusion (40 to 120 cc.) was given. Hematuria increased on the second or third day after the transfusion, but shortly afterward the patient improved. The quickest improvement occurred in nephritis following scarlet fever and in that of unknown origin. The improvement was delayed in nephritis after impetigo. Two patients showed no improvement after transfusion.

FROM THE AUTHOR'S SUMMARY.

TWISTED OVARIAN CYST IN AN INFANT. E. BIÖRKLUND, Svenska läk.-tidning. **42**:105 (Jan. 19) 1945.

A full term, breast-fed female infant who had vomited since birth, fell suddenly ill with increased vomiting and pains in the abdomen. She was first seen two days later in a condition of shock. Her temperature was 38.2 C. (100.8 F.). The abdomen was large, hard and distended, with a tumor in the right iliac fossa. The tentative diagnosis was intussusception, but a colon enema with roentgenographic examination did not verify this diagnosis. At operation a large double twisted cyst of the left ovary filled with sanguinolent fluid was found and extirpated. Histologic examination revealed: cystoma serosum simplex parovarian cyst. The patient was discharged in good condition.

WALLGREN, Stockholm, Sweden.

Miscellaneous

RADIOACTIVE PHOSPHORUS AS A THERAPEUTIC AGENT: A REVIEW OF THE LITERATURE AND ANALYSIS OF THE RESULTS OF TREATMENT OF 155 PATIENTS WITH VARIOUS BLOOD DYSCRASIAS, LYMPHOMAS, AND OTHER MALIGNANT NEOPLASTIC DISEASES. EDWARD H. REINHARD, CARL V. MOORE, OLGA S. BIERBAUM, and SHERWOOD MOORE, J. Lab. & Clin. Med. **31**:107 (Feb.) 1946.

Any brief summary would not do justice to this excellent report; but of the conclusions reached by the authors, the following may be mentioned:

1. Radioactive phosphorus is probably the best therapeutic agent available at present for polycythemia vera.

2. This form of therapy has little effect on the clinical course of acute or subacute myelogenous leukemia, but produces at least as complete clinical and hematologic remissions in the chronic form of the disease as does roentgen radiation. Freedom from radiation sickness is a practical advantage of therapy with radioactive phosphorus.

3. In the great majority of patients the clinical course of acute lymphatic leukemia is not influenced favorably. In treatment of chronic lymphatic leukemia it is probably as satisfactory as, but no better than, roentgen radiation.

4. Hodgkin's disease, lymphosarcoma, reticulum cell sarcoma and multiple myeloma do not respond as favorably to radioactive phosphorus as they do to roentgen radiation.

5. Leukopenia, thrombopenia and anemia may occur as complications of this therapy.

WILKINSON, Galveston, Texas.

MAINTENANCE OF THERAPEUTIC BLOOD CONCENTRATIONS OF PENICILLIN FOR TWENTY-FOUR HOURS FOLLOWING SINGLE INJECTIONS OF PENICILLIN-BEESWAX-PEANUT OIL MIXTURES. WILLIAM M. M. KIRBY, SAMUEL P. MARTIN, WILLIAM LEIFER and MURRAY J. KINSMAN, J. Lab. & Clin. Med. **31**:313 (March) 1946.

The studies described indicate that in most instances effective therapeutic concentrations of penicillin are present in the blood stream for twenty-four hours or longer after single subcutaneous injections of 600,000 units of penicillin suspended in peanut oil and white wax U. S. P. Results following intramuscular injections are somewhat less satisfactory.

WILKINSON, Galveston, Texas.

PRESENT STATE OF CHILDREN'S HOSPITALS AND DEPARTMENTS IN PRAGUE, BOHEMIA AND MORAVIA. A. SYROVATKA, Pediat. listy **1**:137, 1946.

In Prague there are 10 children's hospitals (including 2 clinics and 1 fever hospital) with 2,122 beds. In Bohemia with 15 children's departments (including 2 clinics and fever hospitals), there are 1,391 beds. In Moravia with 12 children's departments (including 2 clinics and fever hospitals), there are 1,382 beds.

FROM THE AUTHOR'S SUMMARY.